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(54) Title: HIGH MOLECULAR WEIGHT SURFACE PROTEINS OF NON-TYPEABLE HAEMOPHILUS

(57) Abstract

High molecular weight surface proteins of non-typeable *Haemophilus influenzae* which exhibit immunogenic properties and genes encoding the same are described. Specifically, genes coding for two immunodominant high molecular weight proteins, HMW1 and HMW2, have been cloned, expressed and sequenced, while genes coding for high molecular proteins HMW3 and HMW4 have been cloned, expressed and partially sequenced.

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SUMMARY OF INVENTION

The inventors, in an effort to further characterize the high molecular weight (HMW) Haemophilus proteins, have cloned, expressed and sequenced the genes coding for two immunodominant HMW proteins (designated HMW1 and HMW2) from a prototype non-typeable Haemophilus strain and have cloned, expressed and almost completely sequenced the genes coding for two additional immunodominant HMW proteins (designated HMW3 and HMW4) from another non-typeable Haemophilus strain.

In accordance with one aspect of the present invention, therefore, there is provided an isolated and purified gene coding for a high molecular weight protein of a non-typeable Haemophilus strain, particularly a gene coding for protein HMW1, HMW2, HMW3 or HMW4, as well as any variant or fragment of such protein which retains the immunological ability to protect against disease caused by a non-typeable Haemophilus strain. In another aspect, the invention provides a high molecular weight protein of non-typeable Haemophilus influenzae which is encoded by these genes.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 is a DNA sequence of a gene coding for protein HMW1 (SEQ ID NO: 1);

Figure 2 is a derived amino acid sequence of protein HMW1 (SEQ ID NO: 2);

Figure 3 is a DNA sequence of a gene coding for protein HMW2 (SEQ ID NO: 3);

Figure 4 is a derived amino acid sequence of HMW2 (SEQ ID NO: 4);

Figure 5A shows restriction maps of representative recombinant phages which contained the HMW1 or HMW2 structural genes, the locations of the structural genes being indicated by the shaded bars;

Figure 5B shows the restriction map of the T7 expression vector pT7-7;

TITLE OF INVENTION

HIGH MOLECULAR WEIGHT SURFACE PROTEINS OF NON-TYPEABLE HAEMOPHILUS

FIELD OF INVENTION

This invention relates to high molecular weight proteins of non-typeable haemophilus.

BACKGROUND TO THE INVENTION

Non-typeable Haemophilus influenzae are non-encapsulated organisms that are defined by their lack of reactivity with antisera against known H. influenzae capsular antigens.

These organisms commonly inhabit the upper respiratory tract of humans and are frequently responsible for infections, such as otitis media, sinusitis, conjunctivitis, bronchitis and pneumonia. Since these organisms do not have a polysaccharide capsule, they are not controlled by the present Haemophilus influenzae type b (Hib) vaccines, which are directed towards Hib bacterial capsular polysaccharid s. The non-typeable strains, however, do produce surface antigens that can elicit bactericidal antibodies. Two of the major outer membrane proteins, P2 and P6, have been identified as targets of human serum bactericidal activity. However, it has been shown that the P2 protein sequence is variable, in particular in the non-typeable Haemophilus strains. Thus, a P2-based vaccine would not protect against all strains of the organism.

There have previously been identified by Barenkamp et al (Pediatr. Infect. Dis. J., 9:333-339, 1990) a group of high-molecular-weight (HMW) proteins that appeared to be major targets of antibodies present in human convalescent sera. Examination of a series of middle ear isolates revealed the presence of one or two such proteins in most strains. However, prior to the present invention, th structures of these proteins were unknown as were pure isolates of such proteins.

antigenically-related proteins are produced by the majority of the non-typeable strains of Haemophilus. Antisera raised against the protein expressed by the HMW1 gene recognizes both the HMW2 protein and the B. pertussis FHA. The present invention includes an isolated and purified high molecular weight protein of non-typeable haemophilus which is antigenically related to the B. pertussis FHA, which may be obtained from natural sources or produced recombinantly.

A phage genomic library of a known strain f non-typeable Haemophilus was prepared by standard methods and the library was screened for clones expressing high molecular weight proteins, using a high titre antiserum against HMW's. A number of strongly reactive DNA clones were plaque-purified and sub-cloned into a T7 expression plasmid. It was found that they all expressed either one or the other of the two high-molecular-weight proteins designated HMW1 and HMW2, with apparent molecular weights of 125 and 120 kDa, respectively, encoded by open reading frames of 4.6 kb and 4.4 kb, respectively.

Representative clones expressing either HMW1 or HMW2 were further characterized and the genes isolated, purified and sequenced. The DNA sequence of HMW1 is shown in Figure 1 and the corresponding derived amino acid sequence in Figure 2. Similarly, the DNA sequence of HMW2 is shown in Figure 3 and the corresponding derived amino acid sequence in Figure 4. Partial purification of the isolated proteins and N-terminal sequence analysis indicated that the expressed proteins are truncated since their sequence starts at residue number 442 of both full length HMW1 and HMW2 gene products.

Subcloning studies with respect to the hmw1 and hmw2 genes indicated that correct processing of the HMW proteins required the products of additional downstream genes. It has been found that both the hmw1 and hmw2 genes are flanked by two additional downstream open

Figure 6 contains the DNA sequence of a gene cluster for the hmw1 gene (SEQ ID NO: 5), comprising nucleotides 351 to 4958 (ORF a) (as in Figure 1), as well as two additional downstream genes in the 3' flanking region, comprising ORFs b, nucleotides 5114-6748 and c nucleotides 7062-9011;

Figure 7 contains the DNA sequence of a gene cluster for the hmw2 gene (SEQ ID NO: 6), comprising nucleotides 792 to 5222 (ORF a) (as in Figure 3), as well as two additional downstream genes in the 3' flanking region, comprising ORFs b, nucleotides 5375-7009, and c, nucleotides 7249-9198;

Figure 8 is a partial DNA sequence of a gene coding for protein HMW3 (SEQ ID NO: 7);

Figure 9 is a partial DNA sequence of a gene coding for protein HMW4 (SEQ ID NO: 8); and

Figure 10 is a comparison table for the derived amino acid sequence for proteins HMW1, HMW2, HMW3 and HMW4.

GENERAL DESCRIPTION OF INVENTION

The DNA sequences of the genes coding for HMW1 and HMW2, shown in Figures 1 and 3 respectively, were shown to be about 80% identical, with the first 1259 base pairs of the genes being identical. The derived amino acid sequences of the two HMW proteins, shown in Figures 2 and 4 respectively, are about 70% identical. Furthermore, the encoded proteins are antigenically related to the filamentous hemagglutinin surface protein of Bordetella pertussis. A monoclonal antibody prepared against filamentous hemagglutinin (FHA) of Bordetella pertussis was found to recognize both of the high molecular weight proteins. This data suggests that the HMW and FHA proteins may serve similar biological functions. The derived amino acid sequences of the HMW1 and HMW2 proteins show sequence similarity to that for the FHA protein. It has further been shown that these

reading frames (ORFs), designated b and c, respectively, (see Figures 6 and 7).

The b ORFs are 1635 bp in length, extending from nucleotides 5114 to 6748 in the case of hmw1 and nucleotides 5375 to 7009 in the case of hmw2, with their derived amino acid sequences 99% identical. The derived amino acid sequences demonstrate similarity with the derived amino acid sequences of two genes which encod proteins required for secretion and activation of hemolysins of P. mirabilis and S. marcescens.

The c ORFs are 1950 bp in length, extending from nucleotides 7062 to 9011 in the case of hmw1 and nucleotides 7249 to 9198 in the case of hmw2, with their derived amino acid sequences 96% identical. The hmw1 c ORF is preceded by a series of 9 bp direct tandem repeats. In plasmid subclones, interruption of the hmw1 b or c ORF results in defective processing and secretion of the hmw1 structural gene product.

The two high molecular weight proteins have been isolated and purified and shown to be partially protective against otitis media in chinchillas and t function as adhesins. These results indicate the potential for use of such high molecular proteins and structurally-related proteins of other non-typeable strains of Haemophilus influenzae as components in non-typeable Haemophilus influenzae vaccines.

Since the proteins provided herein are good cross-reactive antigens and are present in the majority of non-typeable Haemophilus strains, it is evident that these HMW proteins may become integral constituents of a universal Haemophilus vaccine. Indeed, these proteins may be used not only as protective antigens against otitis, sinusitis and bronchitis caused by the non-typeable Haemophilus strains, but also may be used as carriers for the protective Hib polysaccharides in a conjugate vaccine against meningitis. The proteins also

may be used as carriers for other antigens, haptens and polysaccharides from other organisms, so as to induce immunity to such antigens, haptens and polysaccharides.

The nucleotide sequences enccding two high molecular weight proteins of a different non-typeable Haemophilus strain (designated HMW3 and HMW4) have been largely elucidated, and are presented in Figures 8 and 9. HMW3 has an apparent molecular weight of 125 kDa while HMW4 has an apparent molecular weight of 123 kDa. These high molecular weight proteins are antigenically related to the HMW1 and HMW2 proteins and to FHA. Sequence analysis of HMW3 is approximately 85% complete and of HMW4 95% complete, with short stretches at the 5'-ends of each gene remaining to be sequenced.

Figure 10 contains a multiple sequence comparison of the derived amino acid sequences for the four high molecular weight proteins identified herein. As may be seen from this comparison, stretches of identical peptide sequence may be found throughout the length of the comparison, with HMW3 more closely resembling HMW1 and HMW4 more closely resembling HMW2. This information is highly suggestive of a considerable sequence homology between high molecular weight proteins from various non-typeable Haemophilus strains.

In addition, mutants of non-typeable H. influenzae strains that are deficient in expression of HMW1 or HMW2 or both have been constructed and examined for their capacity to adhere to cultured human epithelial cells. The hmw1 and hmw2 gene clusters have been expressed in E. coli and have been examined for in vitro adherence. The results of such experimentation demonstrate that both HMW1 and HMW2 mediate attachment and hence are adhesins and that this function is present even in the absence of other H. influenzae surface structures.

With the isolation and purification of th high molecular weight proteins, the inventors are able to

determine the major protective epitopes by conventional epitope mapping and synth size peptides corresp nding to these determinants to be incorporated in fully synthetic or recombinant vaccines. Accordingly, the invention also comprises a synthetic peptide having an amino acid sequence corresponding to at least one protective epitope of a high molecular weight protein of a non-typeable Haemophilus influenzae. Such peptides are of varying length that constitute portions of the high-molecular-weight proteins, that can be used to induce immunity, either directly or as part of a conjugate, against the relative organisms and thus constitute vaccines for protection against the corresponding diseases.

The present invention also provides any variant or fragment of the proteins that retains the potential immunological ability to protect against disease caused by non-typeable Haemophilus strains. The variants may be constructed by partial deletions or mutations of the genes and expression of the resulting modified genes t give the protein variations.

EXAMPLES

Example 1:

Non-typeable H.influenzae strains 5 and 12 were isolated in pure culture from the middle ear fluid of children with acute otitis media. Chromosomal DNA from strain 12, providing genes encoding proteins HMW1 and HMW2, was prepared by preparing Sau3A partial restriction digests of chromosomal DNA and fractionating on sucrose gradients. Fractions containing DNA fragments in the 9 to 20 kbp range were pooled and a library was prepared by ligation into λEMBL3 arms. Ligation mixtures wer packaged in vitro and plate-amplified in a P2 lysogen of E. coli LE392.

For plasmid subcloning studi s, DNA from a representative recombinant phage was subcloned into the

T7 expression plasmid pT7-7, containing the T7 RNA polymerase promoter Φ10, a ribosome-binding sit and the translational start site for the T7 gene 10 protein upstream from a multiple cloning site (see Figure 5B).

DNA sequence analysis was performed by the dideoxy method and both strands of the HMW1 gene and a single strand of the HMW2 gene were sequenced.

Western immunoblot analysis was performed to identify the recombinant proteins being produced by reactive phage clones. Phage lysates grown in LE392 cells or plaques picked directly from a lawn of LE392 cells on YT plates were solubilized in gel electrophoresis sample buffer prior to electrophoresis. Sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis was performed on 7.5% or 11% polyacrylamide modified Laemmli gels. After transfer of the proteins to nitrocellulose sheets, the sheets were probed sequentially with an E. coli-absorbed human serum sample containing high-titer antibody to the high-molecular-weight proteins and then with alkaline phosphatase-conjugated goat anti-human immunoglobulin G (IgG) second antibody. Sera from healthy adults contains high-titer antibody directed against surface-exposed high-molecular-weight proteins of non-typeable H. influenzae. One such serum sample was used as the screening antiserum after having been extensively absorbed with LE392 cells.

To identify recombinant proteins being produced by E. coli transformed with recombinant plasmids, the plasmids of interest were used to transform E. coli BL21 (DE3)/pLysS. The transformed strains were grown to an A_{600} of 0.5 in L broth containing 50 μg of ampicillin per ml. IPTG was then added to 1 mM. One hour later, cells were harvested, and a sonicate of the cells was prepared. The protein concentrations of the samples wer determined by th bicinchoninic acid method. Cell sonicates

containing 100 μg f total protein were solubilized in electrophoresis sampl buffer, subjected to SDS-polyacrylamide gel electrophoresis, and transferred to nitrocellulose. The nitrocellulose was then probed sequentially with the E. coli-absorbed adult serum sample and then with alkaline phosphatase-conjugated goat anti-human IgG second antibody.

Western immunoblot analysis also was performed to determine whether homologous and heterologous non-typeable H. influenzae strains expressed high-molecular-weight proteins antigenically related to the protein encoded by the cloned HMW1 gene (rHMW1). Cell sonicates of bacterial cells were solubilized in electrophoresis sample buffer, subjected to SDS-polyacrylamide gel electrophoresis, and transferred to nitrocellulose. Nitrocellulose was probed sequentially with polyclonal rabbit rHMW1 antiserum and then with alkaline phosphatase-conjugated goat anti-rabbit IgG second antibody.

Finally, Western immunoblot analysis was performed to determine whether non-typeable Haemophilus strains expressed proteins antigenically related to the filamentous hemagglutinin protein of Bordetella pertussis. Monoclonal antibody X3C, a murine immunoglobulin G (IgG) antibody which recognizes filamentous hemagglutinin, was used to probe cell sonicates by Western blot. An alkaline phosphatase-conjugated goat anti-mouse IgG second antibody was used for detection.

To generate recombinant protein antiserum, E. coli BL21(DE3)/pLysS was transformed with pHMW1-4, and expression of recombinant protein was induced with IPTG, as described above. A cell sonicate of the bacterial cells was prepared and separated into a supernatant and pellet fraction by centrifugation at 10,000 x g f r 30 min. The rec mbinant protein fractionated with the

pellet fraction. A rabbit was subcutaneously immunized on biweekly schedule with 1 mg of protein from the pellet fraction, the first dose given with Freund's complete adjuvant and subsequent doses with Freund's incomplete adjuvant. Following the fourth injection, the rabbit was bled. Prior to use in the Western blot assay, the antiserum was absorbed extensively with sonicates of the host E. coli strain transformed with cloning vector alone.

To assess the sharing of antigenic determinants between HMW1 and filamentous hemagglutinin, enzyme-linked immunosorbent assay (ELISA) plates (Costar, Cambridge, Mass.) were coated with 60 μl of a 4-ug/ml solution of filamentous hemagglutinin in Dulbecco's phosphate-buffered saline per well for 2 h at room temperature. Wells were blocked for 1 h with 1% bovine serum albumin in Dulbecco's phosphate-buffered saline prior to addition of serum dilutions. rHMW1 antiserum was serially diluted in 0.1% Brij (Sigma, St. Louis, Mo.) in Dulbecco's phosphate-buffered saline and incubated for 3 h at room temperature. After being washed, the plates were incubated with peroxidase-conjugated goat anti-rabbit IgG antibody (Bio-Rad) for 2 h at room temperature and subsequently developed with 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (Sigma) at a concentration of 0.54 in mg/ml in 0.1 M sodium citrate buffer, pH 4.2, containing 0.03% H_2O_2. Absorbances were read on an automated ELISA reader.

Recombinant phage expressing HMW1 or HMW2 were recovered as follows. The non-typeable H. influenzae strain 12 genomic library was screened for clones expressing high-molecular-weight proteins with an E. coli-absorbed human serum sample containing a high titer of antibodies directed against the high-molecular-weight proteins.

Numerous strongly reactive clones were identified along with more weakly reactive ones. Twenty strongly reactive clones were plaque-purified and examined by Western blot for expression of recombinant proteins. Each of the strongly reactive clones expressed one of two types of high-molecular-weight proteins, designated HMW1 and HMW2. The major immunoreactive protein bands in the HMW1 and HMW2 lysates migrated with apparent molecular masses of 125 and 120 kDa, respectively. In addition to the major bands, each lysate contained minor protein bands of higher apparent molecular weight. Protein bands seen in the HMW2 lysates at molecular masses of less than 120 kDa were not regularly observed and presumably represent proteolytic degradation products. Lysates of LE392 infected with the λEMBL3 cloning vector alone were non-reactive when immunologically screened with the same serum sample. Thus, the observed activity was not due to cross-reactive E. coli proteins or λEMBL3-encoded proteins. Furthermore, the recombinant proteins were not simply binding immunoglobulin nonspecifically, since the proteins were not reactive with the goat anti-human IgG conjugate alone, with normal rabbit sera, or with serum from a number of healthy young infants.

Representative clones expressing either the HMW1 or HMW2 recombinant proteins were characterized further. The restriction maps of the two phage types were different from each other, including the regions encoding the HMW1 and HMW2 structural genes. Figure 5A shows restriction maps of representative recombinant phage which contained the HMW1 or HMW2 structural genes. The locations of the structural genes are indicated by the shaded bars.

HMW1 plasmid subclones were constructed by using the T7 expression plasmid T7-7 (Fig. 5A and B). HMW2 plasmid subclones also were constructed, and the results with

these latter subclones were similar to those observed with the HMW1 constructs.

The approximate location and direction of transcription of the HMW1 structure gene were initially determined by using plasmid pHMW1 (Fig. 5A). This plasmid was constructed by inserting the 8.5-kb BamHI-SalI fragment from λHMW1 into BamHI- and SalI-cut pT7-7. E. coli transformed with pHMW1 expressed an immunoreactive recombinant protein with an apparent molecular mass of 115 kDa, which was strongly inducible with IPTG. This protein was significantly smaller than the 125-kDa major protein expressed by the parent phage, indicating that it either was being expressed as a fusion protein or was truncated at the carboxy terminus.

To more precisely localize the 3′ end of the structural gene, additional plasmids were constructed with progressive deletions from the 3′ end of the pHMW1 construct. Plasmid pHMW1-1 was constructed by digestion of pHMW1 with PstI, isolation of the resulting 8.8-kb fragment, and religation. Plasmid pHMW1-2 was constructed by digestion of pHMW1 with HindIII, isolation of the resulting 7.5-kb fragment, and religation. E. coli transformed with either plasmid pHMW1-1 or pHMW1-2 also expressed an immunoreactive recombinant protein with an apparent molecular mass of 115 kDa. These results indicated that the 3′ end of the structural gene was 5′ of the HindIII site.

To more precisely localize the 5′ end of the gene, plasmids pHMW1-4 and pHMW1-7 were constructed. Plasmid pHMW1-4 was constructed by cloning the 5.1-kb BamHI-HindIII fragment from λHMW1 into a pT7-7-derived plasmid containing the upstream 3.8-kb EcoRI-BamHi fragment. E. coli transformed with pHMW1-4 expressed an immunoreactive protein with an apparent molecular mass of approximately 160 kDa. Although protein production was inducible with IPTG, the l vels of protein production in these

transformants were substantially lower than those with the pHMW1-2 transformants described above. Plasmid pHMW1-7 was constructed by digesting pHMW1-4 with NdeI and SpeI. The 9.0-kbp fragment generated by this double digestion was isolated, blunt ended, and religated. E. coli transformed with pHMW1-7 also expressed an immunoreactive protein with an apparent molecular mass of 160 kDa, a protein identical in size to that expressed by the pHMW1-4 transformants. The result indicated that the initiation codon for the HMW1 structural gene was 3′ f the SpeI site. DNA sequence analysis confirmed this conclusion.

As noted above, the λHMW1 phage clones expressed a major immunoreactive band of 125 kDa, whereas the HMW1 plasmid clones pHMW1-4 and pHMW1-7, which contained what was believed to be the full-length gene, expressed an immunoreactive protein of approximately 160 kDa. This size discrepancy was disconcerting. One possibl explanation was that an additional gene or genes necessary for correct processing of the HMW1 gene product were deleted in the process of subcloning. To address this possibility, plasmid pHMW1-14 was constructed. This construct was generated by digesting pHMW1 with NdeI and MluI and inserting the 7.6-kbp NdeI-MluI fragment isolated from pHMW1-4. Such a construct would contain the full-length HMW1 gene as well as the DNA 3′ of the HMW1 gene which was present in the original HMW1 phage. E. coli transformed with this plasmid expressed major immunoreactive proteins with apparent molecular masses of 125 and 160 kDa as well as additional degradation products. The 125- and 160-kDa bands were identical to the major and minor immunoreactive bands detected in the HMW1 phage lysates. Interestingly, the pHMW1-14 construct also expressed significant amounts of protein in the uninduced condition, a situation not observed with the arlier constructs.

The relationship between the 125- and 160-kDa proteins remains somewhat unclear. Sequence analysis, described below, reveals that the HMW1 gene would be predicted to encode a protein of 159 kDa. It is believed that the 160-kDa protein is a precursor form of the mature 125-kDa protein, with the conversion from one protein to the other being dependent on the products of the two downstream genes.

Sequence analysis of the HMW1 gene (Figure 1) revealed a 4,608-bp open reading frame (ORF), beginning with an ATG codon at nucleotide 351 and ending with a TAG stop codon at nucleotide 4959. A putative ribosome-binding site with the sequence AGGAG begins 10 bp upstream of the putative initiation codon. Five other in-frame ATG codons are located within 250 bp of the beginning of the ORF, but none of these is preceded by a typical ribosome-binding site. The 5′-flanking region of the ORF contains a series of direct tandem repeats, with the 7-bp sequence ATCTTTC repeated 16 times. These tandem repeats stop 100 bp 5′ of the putative initiation codon. An 8-bp inverted repeat characteristic of a rho-independent transcriptional terminator is present, beginning at nucleotide 4983, 25 bp 3′ of the presumed translational stop. Multiple termination codons are present in all three reading frames both upstream and downstream of the ORF. The derived amino acid sequence of the protein encoded by the HMW1 gene (Figure 2) has a molecular weight of 159,000, in good agreement with the apparent molecular weights of the proteins expressed by the HMW1-4 and HMW1-7 transformants. The derived amino acid sequence of the amino terminus does not demonstrate the characteristics of a typical signal sequence. The BamHI site used in generation of pHMW1 comprises bp 1743 through 1748 of the nucleotide sequence. The ORF downstream of the BamHI site would be predicted to encode a protein of 111 kDa, in good agreement with the 115 kDa

estimated for th apparent molecular mass of the pHMW1-encoded fusion prot in.

The sequence of the HMW2 gene (Figure 3) consists of a 4,431-bp ORF, beginning with an ATG ccdon at nucleotide 352 and ending with a TAG stop codon at nucleotide 4783. The first 1,259 bp of the ORF of the HMW2 gene are identical to those of the HMW1 gene. Thereafter, the sequences begin to diverge but are 80% identical overall. With the exception of a single base addition at nucleotide 93 of the HMW2 sequence, the 5'-flanking regions of the HMW1 and HMW2 genes are identical for 310 bp upstream from the respective initiation codons. Thus, the HMW2 gene is preceded by the same set of tandem repeats and the same putative ribosome-binding site which lies 5' of the HMW1 gene. A putative transcriptional terminator identical to that identified 3' of the HMW1 ORF is noted, beginning at nucleotide 4804. The discrepancy in the lengths of the two genes is principally accounted for by a 186-bp gap in the HMW2 sequence, beginning at nucleotide position 3839. Th derived amino acid sequence of the protein encoded by the HMW2 gene (Figure 4) has a molecular weight of 155,000 and is 71% identical with the derived amino acid sequence of the HMW1 gene.

The derived amino acid sequences of both the HMW1 and HMW2 genes (Figures 2 and 4) demonstrated sequence similarity with the derived amino acid sequence of filamentous hemagglutinin of Bordetella pertussis, a surface-associated protein of this organism. The initial and optimized TFASTA scores for the HMW1-filamentous hemagglutinin sequence comparison were 87 and 186, respectively, with a word size of 2. The z score for the comparison was 45.8. The initial and optimized TFASTA scores for the HMW2-filamentous hemagglutinin sequence comparison were 68 and 196, respectively. The z score for the latter comparison was 48.7. Th magnitudes of

the initial and optimized TFASTA scores and the z scores suggested that a biologically significant relationship existed between the HMW1 and HMW2 gene products and filamentous hemagglutinin. When the derived amino acid sequences of HMW1, HMW2, and filamentous hemagglutinin genes were aligned and compared, the similarities were most notable at the amino-terminal ends of the three sequences. Twelve of the first 22 amino acids in the predicted peptide sequences were identical. In additional, the sequences demonstrated a common five-amino-acid stretch, Asn-Pro-Asn-Gly-Ile, and several shorter stretches of sequence identity within the first 200 amino acids.

Example 2:

To further explore the HMW1-filamentous hemagglutinin relationship, the ability of antiserum prepared against the HMW1-4 recombinant protein (rHMW1) to recognize purified filamentous hemagglutinin was assessed. The rHMW1 antiserum demonstrated ELISA reactivity with filamentous hemagglutinin in a dose-dependent manner. Preimmune rabbit serum had minimal reactivity in this assay. The rHMW1 antiserum also was examined in a Western blot assay and demonstrated weak but positive reactivity with purified filamentous hemagglutinin in this system also.

To identify the native Haemophilus protein corresponding to the HMW1 gene product and to determine the extent to which proteins antigenically related to the HMW1 cloned gene product were common among other non-typeable H. influenzae strains, a panel of Haemophilus strains was screened by Western blot with the rHMW1 antiserum. The antiserum recognized both a 125- and a 120-kDa protein band in the homologous strain 12, the putative mature protein products of the HMW1 and HMW2 g nes, respectively.

When used to screen heterologous non-typ able H. influenzae strains, rHMW1 antiserum recognized high-molecular-weight proteins in 75% of 125 epidemiologically unrelated strains. In general, the antiserum reacted with one or two protein bands in the 100- to 150-kDa range in each of the heterologous strains in a pattern similar but not identical to that seen in the homologous strain.

Monoclonal antibody X3C is a murine IgG antibody directed against the filamentous hemagglutinin protein of B. pertussis. This antibody can inhibit the binding of B. pertussis cells to Chinese hamster ovary cells and HeLa cells in culture and will inhibit hemagglutination of erythrocytes by purified filamentous hemagglutinin. A Western blot assay was performed in which this monoclonal antibody was screened against the same panel of non-typeable H. influenzae strains discussed above. Monoclonal antibody X3C recognized both the high-molecular-weight proteins in non-typeable H. influenza strain 12 which were recognized by the recombinant-protein antiserum. In addition, the monoclonal antibody recognized protein bands in a subset of heterologous non-typeable H. influenzae strains which were identical to those recognized by the recombinant-protein antiserum. On occasion, the filamentous hemagglutinin monoclonal antibody appeared to recognize only one of the two bands which had been recognized by the recombinant-protein antiserum. Overall, monoclonal antibody X3C recognized high-molecular-weight protein bands identical to those recognized by the rHMW1 antiserum in approximately 35% of our collection of non-typeable H. influenzae strains.

Example 3:

Mutants deficient in expression of HMW1, MW2 or both proteins were constructed to examine the role of these proteins in bacterial adherence. The following strategy was employed. pHMW1-14 (see Example 1, Figure 5A) was

digested with BamHI and then ligated to a kanamycin cassette isolated on a 1.3-kb BamHl fragment from pUC4K. The resultant plasmid (pHMW1-17) was linearized by digestion with XbaI and transformed into non-typeable H. influenzae strain 12, followed by selection for kanamycin resistant colonies. Southern analysis of a series of these colonies demonstrated two populations of transformants, one with an insertion in the HMW1 structural gene and the other with an insertion in the HMW2 structural gene. One mutant from each of these classes was selected for further studies.

Mutants deficient in expression of both proteins were recovered using the following protocol. After deletion of the 2.1-kb fragment of DNA between two EcoRI sites spanning the 3'-portion of the HMW1 structural gene in pHMW-15, the kanamycin cassette from pUC4K was inserted as a 1.3-kb EcoRl fragment. The resulting plasmid (pHMW1-16) was linearized by digestion with XbaI and transformed into strain 12, followed again by selection for kanamycin resistant colonies. Southern analysis of a representative sampling of these colonies demonstrated that in seven of eight cases, insertion into both the HMW1 and HMW2 loci had occurred. One such mutant was selected for further studies.

To confirm the intended phenotypes, the mutant strains were examined by Western blot analysis with a polyclonal antiserum against recombinant HMW1 protein. The parental strain expressed both the 125-kD HMW1 and the 120-kD HMW2 protein. In contrast, the HMW2⁻ mutant failed to express the 120-kD protein, and the HMW1 mutant failed to express the 125-kD protein. The double mutant lacked expression of either protein. On the basis of whole cell lysates, outer membrane profiles, and colony morphology, the wild type strain and the mutants were otherwise identical with one another. Transmission

electron microscopy demonstrated that none of the four strains expressed pili.

The capacity of wild type strain 12 to adhere to Chang epithelial cells was examined. In such assays, bacteria were inoculated into broth and allowed to grow to a density of ~2 x 10^9 cfu/ml. Approximately 2 x 10^7 cfu were inoculated onto epithelial cell monolayers, and plates were gently centrifuged at 165 x g for 5 minutes to facilitate contact between bacteria and the epithelial surface. After incubation for 30 minutes at 37°C in 5% CO_2, monolayers were rinsed 5 times with PBS to remov nonadherent organisms and were treated with trypsin-EDTA (0.05% trypsin, 0.5% EDTA) in PBS to release them fr m the plastic support. Well contents were agitated, and dilutions were plated on solid medium to yield the numb r of adherent bacteria per monolayer. Percent adherenc was calculated by dividing the number of adherent cfu per monolayer by the number of inoculated cfu.

As depicted in Table 1 below (the Tables appear at the end of the descriptive text), this strain adher d quite efficiently, with nearly 90% of the inoculum binding to the monolayer. Adherence by the mutant expressing HMW1 but not HMW2 (HMW2$^-$) was also quite efficient and comparable to that by the wild type strain. In contrast, attachment by the strain expressing HMW2 but deficient in expression of HMW1 (HMW1$^-$) was decreased about 15-fold relative to the wild type. Adherence by the double mutant (HMW1$^-$/HMW2$^-$) was decreased even further, approximately 50-fold compared with the wild type and approximately 3-fold compared with the HMW1 mutant. Considered together, these results suggest that both the HMW1 protein and the, HMW2 protein influence attachment to Chang epithelial cells. Interestingly, optimal adherence to this cell line appears to require HMW1 but n t HMW2.

Example 4:

Using the plasmids pHMW1-16 and pHMW1-17 (see Example 3) and following a scheme similar to that employed with strain 12 as described in Example 3, three non-typeable Haemophilus strain 5 mutants were isolated, including one with the kanamycin gene inserted into the hmw1-like (designated hmw3) locus, a second with an insertion in the hmw2-like (designated hmw4) locus, and a third with insertions in both loci. As predicted, Western immunoblot analysis demonstrated that the mutant with insertion of the kanamycin cassette into the hmw1-like locus had lost expression of the HMW3 125-kD protein, while the mutant with insertion into the hmw2-like locus failed to express the HMW4 123-kD protein. The mutant with a double insertion was unable to express either of the high molecular weight proteins.

As shown in Table 1 below, wild type strain 5 demonstrated high level adherence, with almost 80% of the inoculum adhering per monolayer. Adherence by the mutant deficient in expression of the HMW2-like protein was also quite high. In contrast, adherence by the mutant unable to express the, HMW1-like protein was reduced about 5-fold relative to the wild type, and attachment by the double mutant was diminished even further (approximately 25-fold). Examination of Giemsa-stained samples confirmed these observations (not shown). Thus, the results with strain 5 corroborate the findings with strain 12 and the HMW1 and HMW2 proteins.

Example 5:

To confirm an adherence function for the HMW1 and HMW2 proteins and to examine the effect of HMW1 and HMW2 independently of other H. influenzae surface structures, the hmw1 and the hmw2 gene clusters were introduced into E. coli DH5α, using plasmids pHMW1-14 and pHMW2-21, respectively. As a control, the cloning vector, pT7-7, was also transformed into E. coli DH5α. Western blot

analysis demonstrated that E. coli DH5α containing the hmw1 g nes expressed a 125 kDa pr tein, while the same strain harboring the hmw2 genes expressed a 120-kDa protein. E. coli DH5α containing pT7-7 failed to react with antiserum against recombinant HMW1. Transmission electron microscopy revealed no pili or other surface appendages on any of the E. coli strains.

Adherence by the E. coli strains was quantitated and compared with adherence by wild type non-typeable H. influenzae strain 12. As shown in Table 2 below, adherence by E. coli DH5α containing vector alone was less than 1% of that for strain 12. In contrast, E. coli DH5α harboring the hmw1 gene cluster demonstrat d adherence levels comparable to those for strain 12. Adherence by E. coli DH5α containing the hmw2 genes was approximately 6-fold lower than attachment by strain 12 but was increased 20-fold over adherence by E. coli DH5α with pT7-7 alone. These results indicate that the HMW1 and HMW2 proteins are capable of independently mediating attachment to Chang conjunctival cells. These results are consistent with the results with the H. influenzae mutants reported in Examples 3 and 4, providing further evidence that, with Chang epithelial cells, HMW1 is a more efficient adhesin than is HMW2.

Experiments with E. coli HB101 harboring pT7-7, pHMW1-14, or pHMW2-21 confirmed the results obtained with the DH5α derivatives (see Table 2).

Example 6:

HMW1 and HMW2 were isolated and purified from non-typeable H. influenzae (NTHI) strain 12 in the following manner. Non-typeable Haemophilus bacteria from frozen stock culture were streaked onto a chocolate plate and grown overnight at 37°C in an incubator with 5% CO_2. 50ml starter culture of brain heart infusion (BHI) broth, supplemented with 10 μg/ml each of hemin and NAD was inoculated with growth on chocolate plate. The starter

culture was grown until the optical density (O.D. - 600nm) reached 0.6 to 0.8 and then the bacteria in the starter culture was used to inoculate six 500 ml flasks of supplemented BHI using 8 to 10 ml per flask. The bacteria were grown in 500 ml flasks for an additional 5 to 6 hours at which time the O.D. was 1.5 or greater. Cultures were centrifuged at 10,000 rpm for 10 minutes.

Bacterial pellets were resuspended in a total volume of 250 ml of an extraction solution comprising 0.5 M NaCl, 0.01 M Na_2EDTA, 0.01 M Tris 50 μM 1,10-phenanthroline, pH 7.5. The cells were not sonicated or otherwise disrupted. The resuspended cells were allowed to sit on ice at 0°C for 60 minutes. The resuspended cells were centrifuged at 10,000 rpm for 10 minutes at 4°C to remove the majority of intact cells and cellular debris. The supernatant was collected and centrifuged at 100,000 xg for 60 minutes at 4°C. The supernatant again was collected and dialyzed overnight at 4°C against 0.01 M sodium phosphate, pH 6.0.

The sample was centrifuged at 10,000 rpm for 10 minutes at 4°C to remove insoluble debris precipitated from solution during dialysis. The supernatant was applied to a 10 ml CM Sepharose column which has been pre-equilibrated with 0.01 M sodium phosphate, pH 6. Following application to this column, the column was washed with 0.01 M sodium phosphate. Proteins wer elevated from the column with a 0 - 0.5M KCl gradient in 0.01 M Na phosphate, pH 6 and fractions were collected for gel examination. Coomassie gels of column fractions were carried out to identify those fractions containing high molecular weight proteins. The fractions containing high molecular weight proteins were pooled and concentrated to a 1 to 3 ml volume in preparation for application of sample to gel filtration column.

A Sepharose CL-4B gel filtration column was equilibrated with phosphate-buffered saline, pH 7.5. The

c ncentrated high molecular w ight protein sampl was applied to the gel filtration column and column fractions were collected. Coomassie gels were performed on the column fractions to identify those containing high molecular weight proteins. The column fractions containing high molecular weight proteins were pooled.

The proteins were tested to determine whether th y would protect against experimental otitis media caused by the homologous strain.

Chinchillas received three monthly subcutaneous injections with 40 μg of an HMW1-HMW2 protein mixture in Freund's adjuvant. One month after the last injection, the animals were challenged by intrabullar inoculation with 300 cfu of NTHI strain 12.

Infection developed in 5 of 5 control animals versus 5 of 10 immunized animals. Among infected animals, geometric mean bacterial counts in middle ear fluid 7 days post-challenge were 7.4×10^6 in control animals verus 1.3×10^5 in immunized animals.

Serum antibody titres following immunization were comparable in uninfected and infected animals. However, infection in immunized animals was uniformly associated with the appearance of bacteria down-regulated in expression of the HMW proteins, suggesting bacterial selection in response to immunologic pressure.

Although this data shows that protection following immunization was not complete, this data suggests the HMW adhesin proteins are potentially important protective antigens which may comprise one component of a multi-component NTHI vaccine.

These animal challenge tests wererepeated in Chinchillas at a lower dose challenge than the 300 cfu employed above. In this instance, complete protection was achieved. In these experiments, groups of five animals were immunized with 20 μg of the HMW1-HMW2

mixture on days 1, 28, and 42 in the presence of $AlPO_4$. Blood samples were collected on day 53 to monitor the antibody response. On day 56, the left ear of animals was challenged with about 10 cfu of H. influenzae strain 12. Ear infection was monitored on day 4. Four animals in Group 3 were infected previously by H. influenzae strain 12 and were recovered completely for at least one month before the second challenge. The results are outlined in the following Table A:

TABLE A

Protective ability of HMW protein against non-typeable H. influenzae challenge in chinchilla model

Group (#)	Antigens	Total Animals	Number of Animals Showed Positive Ear Infection		
			Tympano-gram	Otosco-pic Examin-ation	cfu of Bac-teria/ 10 µL
1	HMW	5	0	0	0
2	None	5	5	5	850-3200 (4/5)
3	Convalescent	4	0	0	0

Example 7:

A number of synthetic peptides were derived from HMW1. Antisera then was raised to these peptides. The anti-peptide antisera to peptide HMW1-P5 was shown to recognize HMW1. Peptide HMW1-P5 covers amino acids 1453 to 1481 of HMW1, has the sequence VDEVIEAKRILEKVKDLSDEEREALAKLG (SEQ ID NO:9), and represents bases 1498 to 1576 in Figure 10.

This finding demonstrates that the DNA sequence and the derived protein is being interpreted in the correct

reading frame and that peptides derived from th sequence can be produced which will be immunogenic.

SUMMARY OF DISCLOSURE

In summary of this disclosure, the present invention provides high molecular weight proteins of non-typeable Haemophilus, genes coding for the same and vaccin s incorporating such proteins. Modifications are possibl within the scope of this invention.

Table 1. Effect of mutation of high molecular weight proteins on adherence to Chang epithelial cells by nontypable *H. influenzae*.

Strain	ADHERENCE* % inoculum	ADHERENCE* relative to wild type†
Strain 12 derivatives		
wild type	87.7 ± 5.9	100.0 ± 6.7
HMW1- mutant	6.0 ± 0.9	6.8 ± 1.0
HMW2- mutant	89.9 ± 10.8	102.5 ± 12.3
HMW1-/HMW2- mutant	2.0 ± 0.3	2.3 ± 0.3
Strain 5 derivatives		
wild type	78.7 ± 3.2	100.0 ± 4.1
HMW1-like mutant	15.7 ± 2.6	19.9 ± 3.3
HMW2-like mutant	103.7 ± 14.0	131.7 ± 17.8
double mutant	3.5 ± 0.6	4.4 ± 0.8

* Numbers represent mean (± standard error of the mean) of measurements in triplicate or quadruplicate from representative experiments.

† Adherence values for strain 12 derivatives are relative to strain 12 wild type; values for strain 5 derivatives are relative to strain 5 wild type.

Table 2. Adherence by *E. coli* DH5α and HB101 harboring *hmw1* or *hmw2* gene clusters.

Strain*	Adherence relative to *H. influenzae* strain 12†
DH5α (pT7-7)	0.7 ± 0.02
DH5α (pHMW1-14)	114.2 ± 15.9
DH5α (pHMW2-21)	14.0 ± 3.7
HB101 (pT7-7)	1.2 ± 0.5
HB101 (pHMW1-14)	93.6 ± 15.8
HB101 (pHMW2-21)	3.6 ± 0.9

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* The plasmid pHMW1-14 contains the *hmw1* gene cluster, while pHMW2-21 contains the *hmw2* gene cluster; pT7-7 is the cloning vector used in these constructs.

† Numbers represent the mean (± standard error of the mean) of measurements made in triplicate from representative experiments.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: BARENKAMP, STEPHEN J
ST. GEME III, JOSEPH W

(ii) TITLE OF INVENTION: HIGH MOLECULAR WEIGHT SURFACE PROTEINS OF NON-TYPEABLE HAEMOPHILUS

(iii) NUMBER OF SEQUENCES: 8

(iv) CORRESPONDENCE ADDRESS:
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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: US 08/038,682
(B) FILING DATE: 16-MAR-1993
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(viii) ATTORNEY/AGENT INFORMATION:
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(B) REGISTRATION NUMBER: 22,651
(C) REFERENCE/DOCKET NUMBER: 1038-293

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(B) TELEFAX: (703) 415-0813

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5116 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1536 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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35 40 45

Pro Leu Ser Ala Met Leu Leu Ser Leu Gly Val Thr Ser Ile Pro Gln
50 55 60

Ser Val Leu Ala Ser Gly Leu Gln Gly Met Asp Val Val His Gly Thr
65 70 75 80

Ala Thr Met Gln Val Asp Gly Asn Lys Thr Ile Ile Arg Asn Ser Val
85 90 95

Asp Ala Ile Ile Asn Trp Lys Gln Phe Asn Ile Asp Gln Asn Glu Met
100 105 110

Val Gln Phe Leu Gln Glu Asn Asn Asn Ser Ala Val Phe Asn Arg Val
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Ser Val Asn Gly Gly Ser Ile Ser Leu Leu Ala Gly Gln Lys Ile Thr
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            260                 265                 270

Ile Asn Val Arg Ala Ala Thr Ile Arg Asn Gln Gly Lys Leu Ser Ala
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Asp Ser Val Ser Lys Asp Lys Ser Gly Asn Ile Val Leu Ser Ala Lys
    290                 295                 300

Glu Gly Glu Ala Glu Ile Gly Gly Val Ile Ser Ala Gln Asn Gln Gln
305                 310                 315                 320

Ala Lys Gly Gly Lys Leu Met Ile Thr Gly Asp Lys Val Thr Leu Lys
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Thr Gly Ala Val Ile Asp Leu Ser Gly Lys Glu Gly Gly Glu Thr Tyr
            340                 345                 350

Leu Gly Gly Asp Glu Arg Gly Glu Gly Lys Asn Gly Ile Gln Leu Ala
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Lys Lys Thr Ser Leu Glu Lys Gly Ser Thr Ile Asn Val Ser Gly Lys
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Glu Lys Gly Gly Arg Ala Ile Val Trp Gly Asp Ile Ala Leu Ile Asp
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Ile Ser Leu Gly Ala Gln Gly Asn Ile Asn Ile Thr Ala Lys Gln Asp
565 570 575

Ile Ala Phe Glu Lys Gly Ser Asn Gln Val Ile Thr Gly Gln Gly Thr
580 585 590

Ile Thr Ser Gly Asn Gln Lys Gly Phe Arg Phe Asn Asn Val Ser Leu
595 600 605

Asn Gly Thr Gly Ser Gly Leu Gln Phe Thr Thr Lys Arg Thr Asn Lys
610 615 620

Tyr Ala Ile Thr Asn Lys Phe Glu Gly Thr Leu Asn Ile Ser Gly Lys
625 630 635 640

Val Asn Ile Ser Met Val Leu Pro Lys Asn Glu Ser Gly Tyr Asp Lys
645 650 655

Phe Lys Gly Arg Thr Tyr Trp Asn Leu Thr Ser Leu Asn Val Ser Glu
660 665 670

Ser Gly Glu Phe Asn Leu Thr Ile Asp Ser Arg Gly Ser Asp Ser Ala
675 680 685

Gly Thr Leu Thr Gln Pro Tyr Asn Leu Asn Gly Ile Ser Phe Asn Lys
690 695 700

Asp Thr Thr Phe Asn Val Glu Arg Asn Ala Arg Val Asn Phe Asp Ile
705 710 715 720

Lys Ala Pro Ile Gly Ile Asn Lys Tyr Ser Ser Leu Asn Tyr Ala Ser
725 730 735

Phe Asn Gly Asn Ile Ser Val Ser Gly Gly Gly Ser Val Asp Phe Thr
740 745 750

Leu Leu Ala Ser Ser Ser Asn Val Gln Thr Pro Gly Val Val Ile Asn
755 760 765

Ser Lys Tyr Phe Asn Val Ser Thr Gly Ser Ser Leu Arg Phe Lys Thr
770 775 780

Ser Gly Ser Thr Lys Thr Gly Phe Ser Ile Glu Lys Asp Leu Thr Leu
785 790 795 800

Asn Ala Thr Gly Gly Asn Ile Thr Leu Leu Gln Val Glu Gly Thr Asp
805 810 815

Gly Met Ile Gly Lys Gly Ile Val Ala Lys Lys Asn Ile Thr Phe Glu
820 825 830

Gly Gly Asn Ile Thr Phe Gly Ser Arg Lys Ala Val Thr Glu Ile Glu
835 840 845

Gly Asn Val Thr Ile Asn Asn Asn Ala Asn Val Thr Leu Ile Gly Ser
850 855 860

Asp Phe Asp Asn His Gln Lys Pro Leu Thr Ile Lys Lys Asp Val Ile
865 870 875 880

Ile Asn Ser Gly Asn Leu Thr Ala Gly Gly Asn Ile Val Asn Ile Ala
885 890 895

Gly Asn Leu Thr Val Glu Ser Asn Ala Asn Phe Lys Ala Ile Thr Asn
900 905 910

Phe Thr Phe Asn Val Gly Gly Leu Phe Asp Asn Lys Gly Asn Ser Asn
915 920 925

Ile Ser Ile Ala Lys Gly Gly Ala Arg Phe Lys Asp Ile Asp Asn Ser
930 935 940

Lys Asn Leu Ser Ile Thr Thr Asn Ser Ser Ser Thr Tyr Arg Thr Ile
945 950 955 960

Ile Ser Gly Asn Ile Thr Asn Lys Asn Gly Asp Leu Asn Ile Thr Asn
965 970 975

Glu Gly Ser Asp Thr Glu Met Gln Ile Gly Gly Asp Val Ser Gln Lys
980 985 990

Glu Gly Asn Leu Thr Ile Ser Ser Asp Lys Ile Asn Ile Thr Lys Gln
995 1000 1005

Ile Thr Ile Lys Ala Gly Val Asp Gly Glu Asn Ser Asp Ser Asp Ala
1010 1015 1020

Thr Asn Asn Ala Asn Leu Thr Ile Lys Thr Lys Glu Leu Lys Leu Thr
1025 1030 1035 1040

Gln Asp Leu Asn Ile Ser Gly Phe Asn Lys Ala Glu Ile Thr Ala Lys
1045 1050 1055

Asp Gly Ser Asp Leu Thr Ile Gly Asn Thr Asn Ser Ala Asp Gly Thr
1060 1065 1070

Asn Ala Lys Lys Val Thr Phe Asn Gln Val Lys Asp Ser Lys Ile Ser
1075 1080 1085

Ala Asp Gly His Lys Val Thr Leu His Ser Lys Val Glu Thr Ser Gly
1090 1095 1100

Ser Asn Asn Asn Thr Glu Asp Ser Ser Asp Asn Asn Ala Gly Leu Thr
1105 1110 1115 1120

Ile Asp Ala Lys Asn Val Thr Val Asn Asn Asn Ile Thr Ser His Lys
1125 1130 1135

Ala Val Ser Ile Ser Ala Thr Ser Gly Glu Ile Thr Thr Lys Thr Gly
1140 1145 1150

Thr Thr Ile Asn Ala Thr Thr Gly Asn Val Glu Ile Thr Ala Gln Thr
1155 1160 1165

Gly Ser Ile Leu Gly Gly Ile Glu Ser Ser Ser Gly Ser Val Thr Leu
1170 1175 1180

Thr Ala Thr Glu Gly Ala Leu Ala Val Ser Asn Ile Ser Gly Asn Thr
1185 1190 1195 1200

Val Thr Val Thr Ala Asn Ser Gly Ala Leu Thr Thr Leu Ala Gly Ser
1205 1210 1215

Thr Ile Lys Gly Thr Glu Ser Val Thr Thr Ser Ser Gln Ser Gly Asp
1220 1225 1230

Ile Gly Gly Thr Ile Ser Gly Gly Thr Val Glu Val Lys Ala Thr Glu
1235 1240 1245

Ser Leu Thr Thr Gln Ser Asn Ser Lys Ile Lys Ala Thr Thr Gly Glu
1250 1255 1260

Ala Asn Val Thr Ser Ala Thr Gly Thr Ile Gly Gly Thr Ile Ser Gly
1265 1270 1275 1280

Asn Thr Val Asn Val Thr Ala Asn Ala Gly Asp Leu Thr Val Gly Asn
1285 1290 1295

Gly Ala Glu Ile Asn Ala Thr Glu Gly Ala Ala Thr Leu Thr Thr Ser
1300 1305 1310

Ser Gly Lys Leu Thr Thr Glu Ala Ser Ser His Ile Thr Ser Ala Lys
1315 1320 1325

Gly Gln Val Asn Leu Ser Ala Gln Asp Gly Ser Val Ala Gly Ser Ile
1330 1335 1340

Asn Ala Ala Asn Val Thr Leu Asn Thr Thr Gly Thr Leu Thr Thr Val
1345 1350 1355 1360

Lys Gly Ser Asn Ile Asn Ala Thr Ser Gly Thr Leu Val Ile Asn Ala
1365 1370 1375

Lys Asp Ala Glu Leu Asn Gly Ala Ala Leu Gly Asn His Thr Val Val
1380 1385 1390

Asn Ala Thr Asn Ala Asn Gly Ser Gly Ser Val Ile Ala Thr Thr Ser
1395 1400 1405

Ser Arg Val Asn Ile Thr Gly Asp Leu Ile Thr Ile Asn Gly Leu Asn
1410 1415 1420

Ile Ile Ser Lys Asn Gly Ile Asn Thr Val Leu Leu Lys Gly Val Lys
1425 1430 1435 1440

Ile Asp Val Lys Tyr Ile Gln Pro Gly Ile Ala Ser Val Asp Glu Val
1445 1450 1455

Ile Glu Ala Lys Arg Ile Leu Glu Lys Val Lys Asp Leu Ser Asp Glu
1460 1465 1470

Glu Arg Glu Ala Leu Ala Lys Leu Gly Val Ser Ala Val Arg Phe Ile
1475 1480 1485

Glu Pro Asn Asn Thr Ile Thr Val Asp Thr Gln Asn Glu Phe Ala Thr
1490 1495 1500

Arg Pro Leu Ser Arg Ile Val Ile Ser Glu Gly Arg Ala Cys Phe Ser
1505 1510 1515 1520

Asn Ser Asp Gly Ala Thr Val Cys Val Asn Ile Ala Asp Asn Gly Arg
1525 1530 1535

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4937 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

TAAATATACA AGATAATAAA AATAAATCAA GATTTTTGTG ATGACAAACA ACAATTACAA 60
CACCTTTTTT GCAGTCTATA TGCAAATATT TTAAAAAAAT AGTATAAATC CGCCATATAA 120
AATGGTATAA TCTTTCATCT TTCATCTTTA ATCTTTCATC TTTCATCTTT CATCTTTCAT 180
CTTTCATCTT TCATCTTTCA TCTTTCATCT TTCATCTTTC ATCTTTCATC TTTCATCTTT 240
CACATGAAAT GATGAACCGA GGGAAGGGAG GGAGGGGCAA GAATGAAGAG GGAGCTGAAC 300
GAACGCAAAT GATAAAGTAA TTTAATTGTT CAACTAACCT TAGGAGAAAA TATGAACAAG 360
ATATATCGTC TCAAATTCAG CAAACGCCTG AATGCTTTGG TTGCTGTGTC TGAATTGGCA 420
CGGGGTTGTG ACCATTCCAC AGAAAAAGGC TTCCGCTATG TTACTATCTT TAGGTGTAAC 480
CACTTAGCGT TAAAGCCACT TTCCGCTATG TTACTATCTT TAGGTGTAAC ATCTATTCCA 540
CAATCTGTTT TAGCAAGCGG CTTACAAGGA ATGGATGTAG TACACGGCAC AGCCACTATG 600
CAAGTAGATG GTAATAAAAC CATTATCCGC AACAGTGTTG ACGCTATCAT TAATTGGAAA 660
CAATTTAACA TCGACCAAAA TGAAATGGTG CAGTTTTTAC AAGAAAACAA CAACTCCGCC 720
GTATTCAACC GTGTTACATC TAACCAAATC TCCCAATTAA AAGGGATTTT AGATTCTAAC 780
GGACAAGTCT TTTTAATCAA CCCAAATGGT ATCACAATAG GTAAAGACGC AATTATTAAC 840
ACTAATGGCT TTACGGCTTC TACGCTAGAC ATTTCTAACG AAAACATCAA GGCGCGTAAT 900
TTCACCTTCG AGCAAACCAA AGATAAAGCG CTCGCTGAAA TTGTGAATCA CGGTTTAATT 960
ACTGTCGGTA AAGACGGCAG TGTAAATCTT ATTGGTGGCA AAGTGAAAAA CGAGGGTGTG 1020
ATTAGCGTAA ATGGTGGCAG CATTTCTTTA CTCGCAGGGC AAAAAATCAC CATCAGCGAT 1080
ATAATAAACC CAACCATTAC TTACAGCATT GCCGCGCCTG AAAATGAAGC GGTCAATCTG 1140
GGCGATATTT TTGCCAAAGG CGGTAACATT AATGTCCGTG CTGCCACTAT TCGAAACCAA 1200
GGTAAACTTT CTGCTGATTC TGTAAGCAAA GATAAAAGCG GCAATATTGT TCTTTCCGCC 1260
AAAGAGGGTG AAGCGGAAAT TGGCGGTGTA ATTTCCGCTC AAAATCAGCA AGCTAAAGGC 1320
GGCAAGCTGA TGATTACAGG CGATAAAGTC ACATTAAAAA CAGGTGCAGT TATCGACCTT 1380
TCAGGTAAAG AAGGGGGAGA AACTTACCTT GGCGGTGACG AGCGCGGCGA AGGTAAAAAC 1440
GGCATTCAAT TAGCAAAGAA AACCTCTTTA GAAAAAGGCT CAACCATCAA TGTATCAGGC 1500
AAAGAAAAAG GCGGACGCGC TATTGTGTGG GGCGATATTG CGTTAATTGA CGGCAATATT 1560
AACGCTCAAG GTAGTGGTGA TATCGCTAAA ACCGGTGGTT TTGTGGAGAC ATCGGGGCAT 1620

TATTTATCCA TTGACAGCAA TGCAATTGTT AAAACAAAAG AGTGGTTGCT AGACCCTGAT 1680

GATGTAACAA TTGAAGCCGA AGACCCCCTT CGCAATAATA CCGGTATAAA TGATGAATTC 1740

CCAACAGGCA CCGGTGAAGC AAGCGACCCT AAAAAAAATA GCGAACTCAA AACAACGCTA 1800

ACCAATACAA CTATTTCAAA TTATCTGAAA AACGCCTGGA CAATGAATAT AACGGCATCA 1860

AGAAAACTTA CCGTTAATAG CTCAATCAAC ATCGGAAGCA ACTCCCACTT AATTCTCCAT 1920

AGTAAAGGTC AGCGTGGCGG AGGCGTTCAG ATTGATGGAG ATATTACTTC TAAAGGCGGA 1980

AATTTAACCA TTTATTCTGG CGGATGGGTT GATGTTCATA AAAATATTAC GCTTGATCAG 2040

GGTTTTTTAA ATATTACCGC CGCTTCCGTA GCTTTTGAAG GTGGAAATAA CAAAGCACGC 2100

GACGCGGCAA ATGCTAAAAT TGTCGCCCAG GGCACTGTAA CCATTACAGG AGAGGGAAAA 2160

GATTTCAGGG CTAACAACGT ATCTTTAAAC GGAACGGGTA AAGGTCTGAA TATCATTTCA 2220

TCAGTGAATA ATTTAACCCA CAATCTTAGT GGCACAATTA ACATATCTGG GAATATAACA 2280

ATTAACCAAA CTACGAGAAA GAACACCTCG TATTGGCAAA CCAGCCATGA TTCGCACTGG 2340

AACGTCAGTG CTCTTAATCT AGAGACAGGC GCAAATTTTA CCTTTATTAA ATACATTTCA 2400

AGCAATAGCA AAGGCTTAAC AACACAGTAT AGAAGCTCTG CAGGGGTGAA TTTTAACGGC 2460

GTAAATGGCA ACATGTCATT CAATCTCAAA GAAGGAGCGA AAGTTAATTT CAAATTAAAA 2520

CCAAACGAGA ACATGAACAC AAGCAAACCT TTACCAATTC GGTTTTTAGC CAATATCACA 2580

GCCACTGGTG GGGGCTCTGT TTTTTTTGAT ATATATGCCA ACCATTCTGG CAGAGGGGCT 2640

GAGTTAAAAA TGAGTGAAAT TAATATCTCT AACGGCGCTA ATTTTACCTT AAATTCCCAT 2700

GTTCGCGGCG ATGACGCTTT TAAAATCAAC AAAGACTTAA CCATAAATGC AACCAATTCA 2760

AATTTCAGCC TCAGACAGAC GAAAGATGAT TTTTATGACG GGTACGCACG CAATGCCATC 2820

AATTCAACCT ACAACATATC CATTCTGGGC GGTAATGTCA CCCTTGGTGG ACAAAACTCA 2880

AGCAGCAGCA TTACGGGGAA TATTACTATC GAGAAAGCAG CAAATGTTAC GCTAGAAGCC 2940

AATAACGCCC CTAATCAGCA AAACATAAGG GATAGAGTTA TAAAACTTGG CAGCTTGCTC 3000

GTTAATGGGA GTTTAAGTTT AACTGGCGAA AATGCAGATA TTAAAGGCAA TCTCACTATT 3060

TCAGAAAGCG CCACTTTTAA AGGAAAGACT AGAGATACCC TAAATATCAC CGGCAATTTT 3120

ACCAATAATG GCACTGCCGA AATTAATATA ACACAAGGAG TGGTAAAACT TGGCAATGTT 3180

ACCAATGATG GTGATTTAAA CATTACCACT CACGCTAAAC GCAACCAAAG AAGCATCATC 3240

GGCGGAGATA TAATCAACAA AAAAGGAAGC TTAAATATTA CAGACAGTAA TAATGATGCT 3300

GAAATCCAAA TTGGCGGCAA TATCTCGCAA AAAGAAGGCA ACCTCACGAT TTCTTCCGAT 3360

AAAATTAATA TCACCAAACA GATAACAATC AAAAAGGGTA TTGATGGAGA GGACTCTAGT 3420

TCAGATGCGA CAAGTAATGC CAACCTAACT ATTAAAACCA AAGAATTGAA ATTGACAGAA 3480

GACCTAAGTA TTTCAGGTTT CAATAAAGCA GAGATTACAG CCAAAGATGG TAGAGATTTA 3540

ACTATTGGCA ACAGTAATGA CGGTAACAGC GGTGCCGAAG CCAAAACAGT AACTTTTAAC 3600

AATGTTAAAG ATTCAAAAAT CTCTGCTGAC GGTCACAATG TGACACTAAA TAGCAAAGTG 3660

AAAACATCTA GCAGCAATGG CGGACGTGAA AGCAATAGCG ACAACGATAC CGGCTTAACT 3720

ATTACTGCAA AAAATGTAGA AGTAAACAAA GATATTACTT CTCTCAAAAC AGTAAATATC 3780

ACCGCGTCGG AAAAGGTTAC CACCACAGCA GGCTCGACCA TTAACGCAAC AAATGGCAAA 3840

GCAAGTATTA CAACCAAAAC AGGTGATATC AGCGGTACGA TTTCCGGTAA CACGGTAAGT 3900

GTTAGCGCGA CTGGTGATTT AACCACTAAA TCCGGCTCAA AAATTGAAGC GAAATCGGGT 3960

GAGGCTAATG TAACAAGTGC AACAGGTACA ATTGGCGGTA CAATTTCCGG TAATACGGTA 4020

AATGTTACGG CAAACGCTGG CGATTTAACA GTTGGGAATG GCGCAGAAAT TAATGCGACA 4080

GAAGGAGCTG CAACCTTAAC CGCAACAGGG AATACCTTGA CTACTGAAGC CGGTTCTAGC 4140

ATCACTTCAA CTAAGGGTCA GGTAGACCTC TTGGCTCAGA ATGGTAGCAT CGCAGGAAGC 4200

ATTAATGCTG CTAATGTGAC ATTAAATACT ACAGGCACCT TAACCACCGT GGCAGGCTCG 4260

GATATTAAAG CAACCAGCGG CACCTTGGTT ATTAACGCAA AAGATGCTAA GCTAAATGGT 4320

GATGCATCAG GTGATAGTAC AGAAGTGAAT GCAGTCAACG CAAGCGGCTC TGGTAGTGTG 4380

ACTGCGGCAA CCTCAAGCAG TGTGAATATC ACTGGGGATT TAAACACAGT AAATGGGTTA 4440

AATATCATTT CGAAAGATGG TAGAAACACT GTGCGCTTAA GAGGCAAGGA AATTGAGGTG 4500

AAATATATCC AGCCAGGTGT AGCAAGTGTA GAAGAAGTAA TTGAAGCGAA ACGCGTCCTT 4560

GAAAAAGTAA AAGATTTATC TGATGAAGAA AGAGAAACAT TAGCTAAACT TGGTGTAAGT 4620

GCTGTACGTT TTGTTGAGCC AAATAATACA ATTACAGTCA ATACACAAAA TGAATTTACA 4680

ACCAGACCGT CAAGTCAAGT GATAATTTCT GAAGGTAAGG CGTGTTTCTC AAGTGGTAAT 4740

GGCGCACGAG TATGTACCAA TGTTGCTGAC GATGGACAGC CGTAGTCAGT AATTGACAAG 4800

GTAGATTTCA TCCTGCAATG AAGTCATTTT ATTTTCGTAT TATTTACTGT GTGGGTTAAA 4860

GTTCAGTACG GGCTTTACCC ATCTTGTAAA AAATTACGGA GAATACAATA AAGTATTTTT 4920

AACAGGTTAT TATTATG 4937

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1477 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Asn Lys Ile Tyr Arg Leu Lys Phe Ser Lys Arg Leu Asn Ala Leu
1 5 10 15

Val Ala Val Ser Glu Leu Ala Arg Gly Cys Asp His Ser Thr Glu Lys
20 25 30

Gly Ser Glu Lys Pro Ala Arg Met Lys Val Arg His Leu Ala Leu Lys
35 40 45

Pro Leu Ser Ala Met Leu Leu Ser Leu Gly Val Thr Ser Ile Pro Gln
50 55 60

Ser Val Leu Ala Ser Gly Leu Gln Gly Met Asp Val Val His Gly Thr
65 70 75 80

Ala Thr Met Gln Val Asp Gly Asn Lys Thr Ile Ile Arg Asn Ser Val
85 90 95

Asp Ala Ile Ile Asn Trp Lys Gln Phe Asn Ile Asp Gln Asn Glu Met
100 105 110

Val Gln Phe Leu Gln Glu Asn Asn Asn Ser Ala Val Phe Asn Arg Val
115 120 125

Thr Ser Asn Gln Ile Ser Gln Leu Lys Gly Ile Leu Asp Ser Asn Gly
130 135 140

Gln Val Phe Leu Ile Asn Pro Asn Gly Ile Thr Ile Gly Lys Asp Ala
145 150 155 160

Ile Ile Asn Thr Asn Gly Phe Thr Ala Ser Thr Leu Asp Ile Ser Asn
165 170 175

Glu Asn Ile Lys Ala Arg Asn Phe Thr Phe Glu Gln Thr Lys Asp Lys
180 185 190

Ala Leu Ala Glu Ile Val Asn His Gly Leu Ile Thr Val Gly Lys Asp
195 200 205

Gly Ser Val Asn Leu Ile Gly Gly Lys Val Lys Asn Glu Gly Val Ile
210 215 220

Ser Val Asn Gly Gly Ser Ile Ser Leu Leu Ala Gly Gln Lys Ile Thr
225 230 235 240

Ile Ser Asp Ile Ile Asn Pro Thr Ile Thr Tyr Ser Ile Ala Ala Pro
245 250 255

Glu Asn Glu Ala Val Asn Leu Gly Asp Ile Phe Ala Lys Gly Gly Asn
260 265 270

Ile Asn Val Arg Ala Ala Thr Ile Arg Asn Gln Gly Lys Leu Ser Ala
275 280 285

Asp Ser Val Ser Lys Asp Lys Ser Gly Asn Ile Val Leu Ser Ala Lys
290 295 300

Glu Gly Glu Ala Glu Ile Gly Gly Val Ile Ser Ala Gln Asn Gln Gln
305 310 315 320

Ala Lys Gly Gly Lys Leu Met Ile Thr Gly Asp Lys Val Thr Leu Lys
325 330 335

Thr Gly Ala Val Ile Asp Leu Ser Gly Lys Glu Gly Gly Glu Thr Tyr
340 345 350

Leu Gly Gly Asp Glu Arg Gly Glu Gly Lys Asn Gly Ile Gln Leu Ala
355 360 365

Lys Lys Thr Ser Leu Glu Lys Gly Ser Thr Ile Asn Val Ser Gly Lys
370 375 380

Glu Lys Gly Gly Phe Ala Ile Val Trp Gly Asp Ile Ala Leu Ile Asp
385 390 395 400

Gly Asn Ile Asn Ala Gln Gly Ser Gly Asp Ile Ala Lys Thr Gly Gly
405 410 415

Phe Val Glu Thr Ser Gly His Asp Leu Phe Ile Lys Asp Asn Ala Ile
420 425 430

Val Asp Ala Lys Glu Trp Leu Leu Asp Phe Asp Asn Val Ser Ile Asn
435 440 445

Ala Glu Asp Pro Leu Phe Asn Asn Thr Gly Ile Asn Asp Glu Phe Pro
450 455 460

Thr Gly Thr Gly Glu Ala Ser Asp Pro Lys Lys Asn Ser Glu Leu Lys
465 470 475 480

Thr Thr Leu Thr Asn Thr Thr Ile Ser Asn Tyr Leu Lys Asn Ala Trp
485 490 495

Thr Met Asn Ile Thr Ala Ser Arg Lys Leu Thr Val Asn Ser Ser Ile
500 505 510

Asn Ile Gly Ser Asn Ser His Leu Ile Leu His Ser Lys Gly Gln Arg
515 520 525

Gly Gly Gly Val Gln Ile Asp Gly Asp Ile Thr Ser Lys Gly Gly Asn
530 535 540

Leu Thr Ile Tyr Ser Gly Gly Trp Val Asp Val His Lys Asn Ile Thr
545 550 555 560

Leu Asp Gln Gly Phe Leu Asn Ile Thr Ala Ala Ser Val Ala Phe Glu
565 570 575

Gly Gly Asn Asn Lys Ala Arg Asp Ala Ala Asn Ala Lys Ile Val Ala
580 585 590

Gln Gly Thr Val Thr Ile Thr Gly Glu Gly Lys Asp Phe Arg Ala Asn
595 600 605

Asn Val Ser Leu Asn Gly Thr Gly Lys Gly Leu Asn Ile Ile Ser Ser
610 615 620

Val Asn Asn Leu Thr His Asn Leu Ser Gly Thr Ile Asn Ile Ser Gly
625 630 635 640

Asn Ile Thr Ile Asn Gln Thr Thr Arg Lys Asn Thr Ser Tyr Trp Gln
645 650 655

Thr Ser His Asp Ser His Trp Asn Val Ser Ala Leu Asn Leu Glu Thr
660 665 670

Gly Ala Asn Phe Thr Phe Ile Lys Tyr Ile Ser Ser Asn Ser Lys Gly
675 680 685

Leu Thr Thr Gln Tyr Arg Ser Ser Ala Gly Val Asn Phe Asn Gly Val
690 695 700

Asn Gly Asn Met Ser Phe Asn Leu Lys Glu Gly Ala Lys Val Asn Phe
705 710 715 720

Lys Leu Lys Pro Asn Glu Asn Met Asn Thr Ser Lys Pro Leu Pro Ile
725 730 735

Arg Phe Leu Ala Asn Ile Thr Ala Thr Gly Gly Gly Ser Val Phe Phe
740 745 750

Asp Ile Tyr Ala Asn His Ser Gly Arg Gly Ala Glu Leu Lys Met Ser
755 760 765

Glu Ile Asn Ile Ser Asn Gly Ala Asn Phe Thr Leu Asn Ser His Val
770 775 780

Arg Gly Asp Asp Ala Phe Lys Ile Asn Lys Asp Leu Thr Ile Asn Ala
785 790 795 800

Thr Asn Ser Asn Phe Ser Leu Arg Gln Thr Lys Asp Asp Phe Tyr Asp
805 810 815

Gly Tyr Ala Arg Asn Ala Ile Asn Ser Thr Tyr Asn Ile Ser Ile Leu
820 825 830

Gly Gly Asn Val Thr Leu Gly Gly Gln Asn Ser Ser Ser Ser Ile Thr
835 840 845

Gly Asn Ile Thr Ile Glu Lys Ala Ala Asn Val Thr Leu Glu Ala Asn
850 855 860

Asn Ala Pro Asn Gln Gln Asn Ile Arg Asp Arg Val Ile Lys Leu Gly
865 870 875 880

Ser Leu Leu Val Asn Gly Ser Leu Ser Leu Thr Gly Glu Asn Ala Asp
885 890 895

Ile Lys Gly Asn Leu Thr Ile Ser Glu Ser Ala Thr Phe Lys Gly Lys
900 905 910

Thr Arg Asp Thr Leu Asn Ile Thr Gly Asn Phe Thr Asn Asn Gly Thr
915 920 925

Ala Glu Ile Asn Ile Thr Gln Gly Val Val Lys Leu Gly Asn Val Thr
930 935 940

Asn Asp Gly Asp Leu Asn Ile Thr Thr His Ala Lys Arg Asn Gln Arg
945 950 955 960

Ser Ile Ile Gly Gly Asp Ile Ile Asn Lys Lys Gly Ser Leu Asn Ile
965 970 975

Thr Asp Ser Asn Asn Asp Ala Glu Ile Gln Ile Gly Gly Asn Ile Ser
980 985 990

Gln Lys Glu Gly Asn Leu Thr Ile Ser Ser Asp Lys Ile Asn Ile Thr
995 1000 1005

Lys Gln Ile Thr Ile Lys Lys Gly Ile Asp Gly Glu Asp Ser Ser Ser
1010 1015 1020

Asp Ala Thr Ser Asn Ala Asn Leu Thr Ile Lys Thr Lys Glu Leu Lys
1025 1030 1035 1040

Leu Thr Glu Asp Leu Ser Ile Ser Gly Phe Asn Lys Ala Glu Ile Thr
1045 1050 1055

Ala Lys Asp Gly Arg Asp Leu Thr Ile Gly Asn Ser Asn Asp Gly Asn
1060 1065 1070

Ser Gly Ala Glu Ala Lys Thr Val Thr Phe Asn Asn Val Lys Asp Ser
1075 1080 1085

Lys Ile Ser Ala Asp Gly His Asn Val Thr Leu Asn Ser Lys Val Lys
1090 1095 1100

Thr Ser Ser Ser Asn Gly Gly Arg Glu Ser Asn Ser Asp Asn Asp Thr
1105 1110 1115 1120

Gly Leu Thr Ile Thr Ala Lys Asn Val Glu Val Asn Lys Asp Ile Thr
1125 1130 1135

Ser Leu Lys Thr Val Asn Ile Thr Ala Ser Glu Lys Val Thr Thr Thr
1140 1145 1150

Ala Gly Ser Thr Ile Asn Ala Thr Asn Gly Lys Ala Ser Ile Thr Thr
1155 1160 1165

Lys Thr Gly Asp Ile Ser Gly Thr Ile Ser Gly Asn Thr Val Ser Val
1170 1175 1180

Ser Ala Thr Val Asp Leu Thr Thr Lys Ser Gly Ser Lys Ile Glu Ala
1185 1190 1195 1200

Lys Ser Gly Glu Ala Asn Val Thr Ser Ala Thr Gly Thr Ile Gly Gly
1205 1210 1215

Thr Ile Ser Gly Asn Thr Val Asn Val Thr Ala Asn Ala Gly Asp Leu
1220 1225 1230

Thr Val Gly Asn Gly Ala Glu Ile Asn Ala Thr Glu Gly Ala Ala Thr
1235 1240 1245

Leu Thr Ala Thr Gly Asn Thr Leu Thr Thr Glu Ala Gly Ser Ser Ile
1250 1255 1260

Thr Ser Thr Lys Gly Gln Val Asp Leu Leu Ala Gln Asn Gly Ser Ile
1265 1270 1275 1280

Ala Gly Ser Ile Asn Ala Ala Asn Val Thr Leu Asn Thr Thr Gly Thr
1285 1290 1295

Leu Thr Thr Val Ala Gly Ser Asp Ile Lys Ala Thr Ser Gly Thr Leu
1300 1305 1310

Val Ile Asn Ala Lys Asp Ala Lys Leu Asn Gly Asp Ala Ser Gly Asp
1315 1320 1325

Ser Thr Glu Val Asn Ala Val Asn Ala Ser Gly Ser Gly Ser Val Thr
1330 1335 1340

Ala Ala Thr Ser Ser Ser Val Asn Ile Thr Gly Asp Leu Asn Thr Val
1345 1350 1355 1360

Asn Gly Leu Asn Ile Ile Ser Lys Asp Gly Arg Asn Thr Val Arg Leu
1365 1370 1375

Arg Gly Lys Glu Ile Glu Val Lys Tyr Ile Gln Pro Gly Val Ala Ser
1380 1385 1390

Val Glu Glu Val Ile Glu Ala Lys Arg Val Leu Glu Lys Val Lys Asp
1395 1400 1405

Leu Ser Asp Glu Glu Arg Glu Thr Leu Ala Lys Leu Gly Val Ser Ala
1410 1415 1420

Val Arg Phe Val Glu Pro Asn Asn Thr Ile Thr Val Asn Thr Gln Asn
1425 1430 1435 1440

Glu Phe Thr Thr Arg Pro Ser Ser Gln Val Ile Ile Ser Glu Gly Lys
1445 1450 1455

Ala Cys Phe Ser Ser Gly Asn Gly Ala Arg Val Cys Thr Asn Val Ala
1460 1465 1470

Asp Asp Gly Gln Pro
1475

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9171 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

ACAGCGTTCT CTTAATACTA GTACAAACCC ACAATAAAAT ATGACAAACA ACAATTACAA 60

CACCTTTTTT GCAGTCTATA TGCAAATATT TTAAAAAATA GTATAAATCC GCCATATAAA 120

ATGGTATAAT CTTTCATCTT TCATCTTTCA TCTTTCATCT TTCATCTTTC ATCTTTCATC 180

TTTCATCTTT CATCTTTCAT CTTTCATCTT TCATCTTTCA TCTTTCATCT TTCATCTTTC 240

ACATGAAATG ATGAACCGAG GGAAGGGAGG GAGGGGCAAG AATGAAGAGG GAGCTGAACG 300

AACGCAAATG ATAAAGTAAT TTAATTGTTC AACTAACCTT AGGAGAAAAT ATGAACAAGA 360

TATATCGTCT CAAATTCAGC AAACGCCTGA ATGCTTTGGT TGCTGTGTCT GAATTGGCAC 420

GGGGTTGTGA CCATTCCACA GAAAAAGGCA GCGAAAAACC TGCTCGCATG AAAGTGCGTC 480

ACTTAGCGTT AAAGCCACTT TCCGCTATGT TACTATCTTT AGGTGTAACA TCTATTCCAC 540

AATCTGTTTT AGCAAGCGGC TTACAAGGAA TGGATGTAGT ACACGGCACA GCCACTATGC 600

AAGTAGATGG TAATAAAACC ATTATCCGCA ACAGTGTTGA CGCTATCATT AATTGGAAAC 660

AATTTAACAT CGACCAAAAT GAAATGGTGC AGTTTTTACA AGAAAACAAC AACTCCGCCG 720

TATTCAACCG TGTTACATCT AACCAAATCT CCCAATTAAA AGGGATTTTA GATTCTAACG 780

GACAAGTCTT TTTAATCAAC CCAAATGGTA TCACAATAGG TAAAGACGCA ATTATTAACA 840

CTAATGGCTT TACGGCTTCT ACGCTAGACA TTTCTAACGA AAACATCAAG GCGCGTAATT 900

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(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9323 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

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TCAAAAGGTC AATCTATCTC TGCGAATCTG AAATGGAGTT ATTATCTCCC AACATTTAAC 6180

CTTGGCATGG AAGACCAATT TAAAATTAAT TTAGGCTACA ACTACCGCCA TATTAATCAA 6240

ACCTCCGCGT TAAATCGCTT GGGTGAAACG AAGAAAAAAT TTGCAGTATC AGGCGTAAGT 6300

GCAGGCATTG ATGGACATAT CCAATTTACC CCTAAAACAA TCTTTAATAT TGATTTAACT 6360

CATCATTATT ACGCGAGTAA ATTACCAGGC TCTTTTGGAA TGGAGCGCAT TGGCGAAACA 6420

TTTAATCGCA GCTATCACAT TAGCACAGCC AGTTTAGGGT TGAGTCAAGA GTTTGCTCAA 6480

GGTTGGCATT TTAGCAGTCA ATTATCAGGT CAATTTACTC TACAAGATAT TAGCAGTATA 6540

GATTTATTCT CTGTAACAGG TACTTATGGC GTCAGAGGCT TTAAATACGG CGGTGCAAGT 6600

GGTGAGCGCG GTCTTGTATG GCGTAATGAA TTAAGTATGC CAAAATACAC CCGCTTCCAA 6660

ATCAGCCCTT ATGCGTTTTA TGATGCAGGT CAGTTCCGTT ATAATAGCGA AAATGCTAAA 6720

ACTTACGGCG AAGATATGCA CACGGTATCC TCTGCGGGTT TAGGCATTAA AACCTCTCCT 6780

ACACAAAACT TAAGCCTAGA TGCTTTTGTT GCTCGTCGCT TTGCAAATGC CAATAGTGAC 6840

AATTTGAATG GCAACAAAAA ACGCACAAGC TCACCTACAA CCTTCTGGGG GAGATTAACA 6900

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CGGAATTAAG CAACAATCAA ACTCCCCTGC GAATATTTAA ACAACCACGC AAGCCCAGCC 7260

TATTACGCTT GGAACAACAT ATCGCAAAAA AAGATTATGA GTTTGCTTGT CGTGAATTAA 7320

TGGTGATTCT GGAAAAAATG GACGCTAATT TTGGAGGCGT TCACGATATT GAATTTGACG 7380

CACCCGCTCA GCTGGCATAT CTACCCGAAA AATTACTAAT TTATTTTGCC ACTCGTCTCG 7440

CTAATGCAAT TACAACACTC TTTTCCGACC CCGAATTGGC AATTTCTGAA GAAGGGGCGT 7500

TAAAGATGAT TAGCCTGCAA CGCTGGTTGA CGCTGATTTT TGCCTCTTCC CCCTACGTTA 7560

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TAGCAACAGA CAACTCTTCT ATTGCTAAAT TCTGTATTTT TTACTTACCC GAATCCAATG 7680

TCAATATGAG TTTAGATGCG TTATGGGCAG GGAATCAACA ACTTTGTGCT TCATTGTGTT 7740

TTGCGTTGCA GTCTTCACGT TTTATTGGTA CCGCATCTGC GTTTCATAAA AGAGCGGTGG 7800

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TTGACGAGTT CTTTGAAATC AGTAGCAATA ATATAATGGA GAGACTGTTT TTTATCCGTA 8220

AACAGTGCGA AACTTTCCAA CCCGCAGTGT TCTATATGCC AAGCATTGGC ATGGATATTA 8280

CCACGATTTT TGTGAGCAAC ACTCGGCTTG CCCCTATTCA AGCTGTAGCC CTGGGTCATC 8340

CTGCCACTAC GCATTCTGAA TTTATTGATT ATGTCATCGT AGAAGATGAT TATGTGGGCA 8400

GTGAAGATTG TTTCAGCGAA ACCCTTTTAC GCTTACCCAA AGATGCCCTA CCTTATGTAC 8460

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AAATCAGAGA TAAAGCTAAA GTCAAAATAC ATTTTCATTT CGCACTTGGA CAATCAACAG 8640

GCTTGACACA CCCTTATGTC AAATGGTTTA TCGAAAGCTA TTTAGGTGAC GATGCCACTG 8700

CACATCCCCA CGCACCTTAT CACGATTATC TGGCAATATT GCGTGATTGC GATATGCTAC 8760

TAAATCCGTT TCCTTTCGGT AATACTAACG GCATAATTGA TATGGTTACA TTAGGTTTAG 8820

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GCTTAGGACT ACCAGAATGG CTGATAGCCG ACACACGAGA AACATATATT GAATGTGCTT 8940

TGCGTCTAGC AGAAAACCAT CAAGAACGCC TTGAACTCCG TCGTTACATC ATAGAAAACA 9000

ACGGCTTACA AAAGCTTTTT ACAGGCGACC CTCGTCCATT GGGCAAAATA CTGCTTAAGA 9060

AAACAAATGA ATGGAAGCGG AAGCACTTGA GTAAAAAATA ACGGTTTTTT AAAGTAAAAG 9120

TGCGGTTAAT TTTCAAAGCG TTTTAAAAAC CTCTCAAAAA TCAACCGCAC TTTTATCTTT 9180

ATAACGATCC CGCACGCTGA CAGTTTATCA GCCTCCCGCC ATAAAACTCC GCCTTTCATG 9240

GCGGAGATTT TAGCCAAAAC TGGCAGAAAT TAAAGGCTAA AATCACCAAA TTGCACCACA 9300

AAATCACCAA TACCCACAAA AAA 9323

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4287 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GATCAATCTG GGCGATATTT TTGCCAAAGG TGGTAACATT AATGTCCGCG CTGCCACTAT 60

TCGCAATAAA GGTAAACTTT CTGCCGACTC TGTAAGCAAA GATAAAAGTG GTAACATTGT 120

TCTCTCTGCC AAAGAAGGTG AAGCGGAAAT TGGCGGTGTA ATTTCCGCTC AAAATCAGCA 180

AGCCAAAGGT GGTAAGTTGA TGATTACAGG CGATAAAGTT ACATTGAAAA CGGGTGCACT 240

TATCGACCTT TCGGGTAAAG AAGGGGGAGA AACTTATCTT GGCGGTGACG AGCGTGGCGA 300

AGGTAAAAAC GGCATTCAAT TAGCAAAGAA AACCACTTTA GAAAAAGGCT CAACAATTAA 360

TGTGTCAGGT AAAGAAAAAG CTGGGCGCGC TATTGTATGG GGCGATATTG CGTTAATTGA 420

CGGCAATATT AATGCCCAAG GTAAAGATAT CGCTAAAACT GGTGGTTTTG TGGAGACGTC 480

GGGGCATTAC TTATCCATTG ATGATAACGC AATTGTTAAA ACAAAAGAAT GGCTACTAGA 540

CCCAGAGAAT GTGACTATTG AAGCTCCTTC CGCTTCTCGC GTCGAGCTGG GTGCCGATAG 600

GAATTCCCAC TCGGCAGAGG TGATAAAAGT GACCCTAAAA AAAAATAACA CCTCCTTGAC 660

AACACTAACC AATACAACCA TTTCAAATCT TCTGAAAAGT GCCCACGTGG TGAACATAAC 720

GGCAAGGAGA AAACTTACCG TTAATAGCTC TATCAGTATA GAAAGAGGCT CCCACTTAAT 780

TCTCCACAGT GAAGGTCAGG GCGGTCAAGG TGTTCAGATT GATAAAGATA TTACTTCTGA 840

AGGCGGAAAT TTAACCATTT ATTCTGGCGG ATGGGTTGAT GTTCATAAAA ATATTACGCT 900

TGGTAGCGGC TTTTTAAACA TCACAACTAA AGAAGGAGAT ATCGCCTTCG AAGACAAGTC 960

TGGACGGAAC AACCTAACCA TTACAGCCCA AGGGACCATC ACCTCAGGTA ATAGTAACGG 1020

CTTTAGATTT AACAACGTCT CTCTAAACAG CCTTGGCGGA AAGCTGAGCT TTACTGACAG 1080

CAGAGAGGAC AGAGGTAGAA GAACTAAGGG TAATATCTCA AACAAATTTG ACGGAACGTT 1140

AAACATTTCC GGAACTGTAG ATATCTCAAT GAAAGCACCC AAAGTCAGCT GGTTTTACAG 1200

AGACAAAGGA CGCACCTACT GGAACGTAAC CACTTTAAAT GTTACCTCGG GTAGTAAATT 1260

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ATTAAATGGC ATAACATTTA ATAAAGCCAC TTTTAATATC GCACAAGGCT CAACAGCTAA 1380

CTTTAGCATC AAGGCATCAA TAATGCCCTT TAAGAGTAAC GCTAACTACG CATTATTTAA 1440

TGAAGATATT TCAGTCTCAG GGGGGGGTAG CGTTAATTTC AAACTTAACG CCTCATCTAG 1500

CAACATACAA ACCCCTGGCG TAATTATAAA ATCTCAAAAC TTTAATGTCT CAGGAGGGTC 1560

AACTTTAAAT CTCAAGGCTG AAGGTTCAAC AGAAACCGCT TTTTCAATAG AAAATGATTT 1620

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CGGCTCTCAA AAAGCCACAA CAGAAATCAA AGGCAATGTT ACCATCAATA AAAACACTAA 1800

CGCTACTCTT CGTGGTGCGA ATTTTGCCGA AAACAAATCG CCTTTAAATA TAGCAGGAAA 1860

TGTTATTAAT AATGGCAACC TTACCACTGC CGGCTCCATT ATCAATATAG CCGGAAATCT 1920

TACTGTTTCA AAAGGCGCTA ACCTTCAAGC TATAACAAAT TACACTTTTA ATGTAGCCGG 1980

CTCATTTGAC AACAATGGCG CTTCAAACAT TTCCATTGCC AGAGGAGGGG CTAAATTTAA 2040

AGATATCAAT AACACCAGTA GCTTAAATAT TACCACCAAC TCTGATACCA CTTACCGCAC 2100

CATTATAAAA GGCAATATAT CCAACAAATC AGGTGATTTG AATATTATTG ATAAAAAAAG 2160

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TGATTTAACT ATTGGCAATG CTAGCGGTGG TAATGCTGAT GCTAAAAAAG TGACTTTTGA 2460

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GAAAACGTCT AATGGTAGTA GCAATGCTGG TAATGATAAC AGCACCGGTT TAACCATTTC 2580

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GGAAGTAACT GCTCAAAATG GTACAATTAA AGGCAACATT ACCTCGCAAA ATGTAACAGT 2760

GACAGCAACA GAAAATCTTG TTACCACAGA GAATGCTGTC ATTAATGCAA CCAGCGGCAC 2820

AGTAAACATT AGTACAAAAA CAGGGGATAT TAAAGGTGGA ATTGAATCAA CTTCCGGTAA 2880

TGTAAATATT ACAGCGAGCG GCAATACACT TAAGGTAAGT AATATCACTG GTCAAGATGT 2940

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AACAGGCAAT GCAAATATTA CAACCAAAAC AGGTGATATC AACGGTAAAG TTGAATCCAG 3060

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AGTTGAAGCG AAAAATGGAG CTGCAACCTT AACTGCTGAA TCAGGCAAAT TAACCACCCA 3360

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TATCGCAGGA AACATTAATG CTGCTAATGT GACGTTAAAT ACCACAGGCA CTTTAACTAC 3480

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AATAAATGGG TTAAATATCA TTTCGGAAAA TGGTAGAAAC ACTGTGCGCT TAAGAGGCAA 3720

GGAAATTGAT GTGAAATATA TCCAACCAGG TGTAGCAAGC GTAGAAGAGG TAATTGAAGC 3780

GAAACGCGTC CTTGAGAAGG TAAAAGATTT ATCTGATGAA GAAAGAGAAA CACTAGCCAA 3840

ACTTGGTGTA AGTGCTGTAC GTTTCGTTGA GCCAAATAAT GCCATTACGG TTAATACACA 3900

AAACGAGTTT ACAACCAAAC CATCAAGTCA AGTGACAATT TCTGAAGGTA AGGCGTGTTT 3960

CTCAAGTGGT AATGGCGCAC GAGTATGTAC CAATGTTGCT GACGATGGAC AGCAGTAGTC 4020

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TGTGTGGGTT AAAGTTCAGT ACGGGCTTTA CCCACCTTGT AAAAAATTAC GAAAAATACA 4140

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GCAATATCAA TATTGCTTGG CTTGGCTTCT TCATCGACGT ATGCAGAAGA AGCGTTTTTA 4260

GTAAAAGGCT TTCAGTTATC TGGCGCG 4287

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PCT/CA 99/01189

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		AU 687619 B	26-02-1998
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		US 5962430 A	05-10-1999

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4702 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GGGAATGAGC GTCGTACACG GTACAGCAAC CATGCAAGTA GACGGCAATA AAACCACTAT 60
CCGTAATAGC ATCAATGCTA TCATCAATTG GAAACAATTT AACATTGACC AAAATGAAAT 120
GGAGCAGTTT TTACAAGAAA GCAGCAACTC TGCCGTTTTC AACCGTGTTA CATCTGACCA 180
AATCTCCCAA TTAAAAGGGA TTTTAGATTC TAACGGACAA GTCTTTTTAA TCAACCCAAA 240
TGGTATCACA ATAGGTAAAG ACGCAATTAT TAACACTAAT GGCTTTACTG CTTCTACGCT 300
AGACATTTCT AACGAAAACA TCAAGGCGCG TAATTTCACC CTTGAGCAAA CCAAGGATAA 360
AGCACTCGCT GAAATCGTGA ATCACGGTTT AATTACCGTT GGTAAAGACG GTAGCGTAAA 420
CCTTATTGGT GGCAAAGTGA AAAACGAGGG CGTGATTAGC GTAAATGGCG GTAGTATTTC 480
TTTACTTGCA GGGCAAAAAA TCACCATCAG CGATATAATA AATCCAACCA TCACTTACAG 540
CATTGCTGCA CCTGAAAACG AAGCGATCAA TCTGGGCGAT ATTTTTGCCA AAGGTGGTAA 600
CATTAATGTC CGCGCTGCCA CTATTCGCAA TAAAGGTAAA CTTTCTGCCG ACTCTGTAAG 660
CAAAGATAAA AGTGGTAACA TTGTTCTCTC TGCCAAAGAA GGTGAAGCGG AAATTGGCGG 720
TGTAATTTCC GCTCAAAATC AGCAAGCCAA AGGTGGTAAG TTGATGATTA CAGGTGATAA 780
AGTCACATTA AAAACAGGTG CAGTTATCGA CCTTTCAGGT AAAGAAGGGG GAGAGACTTA 840
TCTTGGCGGT GATGAGCGTG GCGAAGGTAA AAATGGTATT CAATTAGCGA AGAAAACCTC 900
TTTAGAAAAA GGCTCGACAA TTAATGTATC AGGCAAAGAA AAAGGCGGGC GCGCTATTGT 960
ATGGGGCGAT ATTGCATTAA TTAATGGTAA CATTAATGCT CAAGGTAGCG ATATTGCTAA 1020
AACTGGCGGC TTTGTGGAAA CATCAGGACA TGACTTATCC ATTGGTGATG ATGTGATTGT 1080
TGACGCTAAA GAGTGGTTAT TAGACCCAGA TGATGTGTCC ATTGAAACTC TTACATCTGG 1140
ACGCAATAAT ACCGGCGAAA ACCAAGGATA TACAACAGGA GATGGGACTA AAGAGTCACC 1200
TAAAGGTAAT AGTATTTCTA AACCTACATT AACAAACTCA ACTCTTGAGC AAATCCTAAG 1260
AAGAGGTTCT TATGTTAATA TCACTGCTAA TAATAGAATT TATGTTAATA GCTCCATCAA 1320
CTTATCTAAT GGCAGTTTAA CACTTCACAC TAAACGAGAT GGAGTTAAAA TTAACGGTGA 1380
TATTACCTCA AACGAAAATG GTAATTTAAC CATTAAAGCA GGCTCTTGGG TTGATGTTCA 1440
TAAAAACATC ACGCTTGGTA CGGGTTTTTT CAATATTGTC GCTGGGGATT CTGTAGCTTT 1500
TGAGAGAGAG GGCGATAAAG CACGTAACGC AACAGATGCT CAAATTACCG CACAAGGGAC 1560
GATAACCGTC AATAAAGATG ATAAACAATT TAGATTCAAT AATGTATCTA TTAACGGGAC 1620

GGGCAAGGGT TTAAAGTTTA TTGCAAATCA AAATAATTTC ACTCATAAAT TTGATGGCGA 1680

AATTAACATA TCTGGAATAG TAACAATTAA CCAAACCACG AAAAAAGATG TTAAATACTG 1740

GAATGCATCA AAAGACTCTT ACTGGAATGT TTCTTCTCTT ACTTTGAATA CGGTGCAAAA 1800

ATTTACCTTT ATAAAATTCG TTGATAGCGG CTCAAATTCC CAAGATTTGA GGTCATCACG 1860

TAGAAGTTTT GCAGGCGTAC ATTTTAACGG CATCGGAGGC AAAACAAACT TCAACATCGG 1920

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CATTACCGGC GGGCTTGACT TTTCCATAAC ATCCCATAAT CGCAATAGTA ATGCTTTTGA 2160

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TCTTGGCGGC AATGTCACTC TAGGTGGGGA AAATTCAAGC AGTAGCATTA CGGGCAATAT 2340

CAATATCACC AATAAAGCAA ATGTTACATT ACAAGCTGAC ACCAGCAACA GCAACACAGG 2400

CTTGAAGAAA AGAACTCTAA CTCTTGGCAA TATATCTGTT GAGGGGAATT TAAGCCTAAC 2460

TGGTGCAAAT GCAAACATTG TCGGCAATCT TTCTATTGCA GAAGATTCCA CATTTAAAGG 2520

AGAAGCCAGT GACAACCTAA ACATCACCGG CACCTTTACC AACAACGGTA CCGCCAACAT 2580

TAATATAAAA CAAGGAGTGG TAAAACTCCA AGGCGATATT ATCAATAAAG GTGGTTTAAA 2640

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GATAACAATC AAAGCAGGCG TTGAAGGGGG GCGTTCTGAT TCAAGTGAGG CAGAAAATGC 2880

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TGGTAATGAT AACAGCACCG GTTTAACCAT TTCCGCAAAA GATGTAACGG TAAACAATAA 3180

CGTTACCTCC CACAAGACAA TAAATATCTC TGCCGCAGCA GGAAATGTAA CAACCAAAGA 3240

AGGCACAACT ATCAATGCAA CCACAGGCAG CGTGGAAGTA ACTGCTCAAA ATGGTACAAT 3300

TAAAGGCAAC ATTACCTCGC AAAATGTAAC AGTGACAGCA ACAGAAAATC TTGTTACCAC 3360

AGAGAATGCT GTCATTAATG CAACCAGCGG CACAGTAAAC ATTAGTACAA AAACAGGGGA 3420

TATTAAAGGT GGAATTGAAT CAACTTCCGG TAATGTAAAT ATTACAGCGA GCGGCAATAC 3480

ACTTAAGGTA AGTAATATCA CTGGTCAAGA TGTAACAGTA ACAGCGGATG CAGGAGCCTT 3540

GACAACTACA GCAGGCTCAA CCATTAGTGC GACAACAGGC AATGCAAATA TTACAACCAA 3600

AACAGGTGAT ATCAACGGTA AAGTTGAATC CAGCTCCGGC TCTGTAACAC TTGTTGCAAC 3660

TGGAGCAACT CTTGCTGTAG GTAATATTTC AGGTAACACT GTTACTATTA CTGCGGATAG 3720

CGGTAAATTA ACCTCCACAG TAGGTTCTAC AATTAATGGG ACTAATAGTG TAACCACCTC 3780

AAGCCAATCA GGCGATATTG AAGGTACAAT TTCTGGTAAT ACAGTAAATG TTACAGCAAG 3840

CACTGGTGAT TTAACTATTG GAAATAGTGC AAAAGTTGAA GCGAAAAATG GAGCTGCAAC 3900

CTTAACTGCT GAATCAGGCA AATTAACCAC CCAAACAGGC TCTAGCATTA CCTCAAGCAA 3960

TGGTCAGACA ACTCTTACAG CCAAGGATAG CAGTATCGCA GGAAACATTA ATGCTGCTAA 4020

TGTGACGTTA AATACCACAG GCACTTTAAC TACTACAGGG GATTCAAAGA TTAACGCAAC 4080

CAGTGGTACC TTAACAATCA ATGCAAAAGA TGCCAAATTA GATGGTGCTG CATCAGGTGA 4140

CCGCACAGTA GTAAATGCAA CTAACGCAAG TGGCTCTGGT AACGTGACTG CGAAAACCTC 4200

AAGCAGCGTG AATATCACCG GGGATTTAAA CACAATAAAT GGGTTAAATA TCATTTCGGA 4260

AAATGGTAGA AACACTGTGC GCTTAAGAGG CAAGGAAATT GATGTGAAAT ATATCCAACC 4320

AGGTGTAGCA AGCGTAGAAG AGGTAATTGA AGCGAAACGC GTCCTTGAGA AGGTAAAAGA 4380

TTTATCTGAT GAAGAAAGAG AAACACTAGC CAAACTTGGT GTAAGTGCTG TACGTTTCGT 4440

TGAGCCAAAT AATGCCATTA CGGTTAATAC ACAAAACGAG TTTACAACCA AACCATCAAG 4500

TCAAGTGACA ATTTCTGAAG GTAAGGCGTG TTTCTCAAGT GGTAATGGCG CACGAGTATG 4560

TACCAATGTT GCTGACGATG GACAGCAGTA GTCAGTAATT GACAAGGTAG ATTTCATCCT 4620

GCAATGAAGT CATTTTATTT TCGTATTATT TACTGTGTGG GTTAAAGTTC AGTACGGGCT 4680

TTACCCACCT TGTAAAAAAT TA 4702

CLAIMS

What we claim is:

1. A vaccine against disease caused by non-typeable Haemophilus influenzae, including otitis media, sinusitis and bronchitis, comprising an effective amount of a high molecular weight protein of non-typeable Haemophilus influenzae which is protein HMW1, HMW2, HMW3 or HMW4 or a variant or fragment of said protein retaining immunological properties thereof or a synthetic peptide having an amino acid sequence corresponding to that of said protein, and a physiological carrier therefor.

2. The vaccine of claim 1 wherein said protein is HMW1 encoded by the DNA sequence shown in Figure 1 (SEQ ID NO:1), having the derived amino acid sequence of Figur 2 (SEQ ID NO:2) and having an apparent molecular weight of 125 kDa.

3. The vaccine of claim 1 wherein said protein is HMW2 encoding by the DNA sequence shown in Figure 3 (SEQ ID NO:3), having the derived amino acid sequence of Figure 4 (SEQ ID NO:4) and having an apparent molecular weight of 120 kDa.

FIG. 1A. DNA SEQUENCE OF HIGH MOLECULAR WEIGHT PROTEIN I (HMW1)

```
   1  ACAGCGTTCT CTTAATACTA GTACAAACCC ACAATAAAAT ATGACAAACA
  51  ACAATTACAA CACCTTTTTT GCAGTCTATA TGCAAATATT TTAAAAAATA
 101  GTATAAATCC GCCATATAAA ATGGTATAAT CTTTCATCTT TCATCTTTCA
 151  TCTTTCATCT TTCATCTTTC ATCTTTCATC TTTCATCTTT CATCTTTCAT
 201  CTTTCATCTT TCATCTTTCA TCTTTCATCT TTCATCTTTC ACATGCCCTG
 251  ATGAACCGAG GGAAGGGAGG GAGGGGCAAG AATGAAGAGG GAGCTGAACG
 301  AACGCAAATG ATAAAGTAAT TTAATTGTTC AACTAACCTT AGGAGAAAAT
 351  ATGAACAAGC TATATCGTCT CAAATTCAGC AAACGCCTGA ATGCTTTGGT
 401  TGCTGTGTCT GAATTGGCAC GGGGTTGTGA CCATTCCACA GAAAAAGGCA
 451  GCGAAAAACC TGCTCGCATG AAAGTGCGTC ACTTAGCGTT AAAGCCACTT
 501  TCCGCTATGT TACTATCTTT AGGTGTAACA TCTATTCCAC AATCTGTTTT
 551  AGCAAGCGGC TTACAAGGAA TGGATGTAGT ACACGGCACA GCCACTATGC
 601  AAGTAGATGG TAATAAAACC ATTATCCGCA ACAGTGTTGA CGATATCATT
 651  AATTGGAAAC AATTTAACAT CGACCAAAAT GAAATGGTGC AGTTTTTACA
 701  AGAAAACAAC AACTCCGCCG TATTCAACCG TGTTACATCT AACCAAATCT
```

FIG.1B.

```
 751  CCCAATTAAA AGGGATTTTA GATTCTAACG GACAAGTCTT TTTAATCAAC
 801  CCAAATGGTA TCACAATAGG TAAAGACGCA ATTATTAACA CTAATGGCTT
 851  TACGGCTTCT ACGCTAGACA TTTCTAACGA AAACATCAAG GCGCGTAATT
 901  TCACCTTCGA GCAAACCAAA GATAAAGCGC TCGCTGAAAT TGTGAATCAC
 951  GGTTTAATTA CTGTCGGTAA AGACGGCAGT GTAAATCTTA TTGGTGGCAA
1001  AGTGAAAAAC GAGGGTGTGA TTAGCGTAAA TGGTGGCAGC ATTTCTTTAC
1051  TCGCAGGGCA AAAAATCACC ATCAGCGATA TAATAAACCC AACCATTACT
1101  TACAGCATTG CCGCGCCTGA AAATGAAGCG GTCAATCTGG GCGATATTTT
1151  TGCCAAAGGC GGTAACATTA ATGTCCGTGC TGCCACTATT CGAAACCAAG
1201  GTAAACTTTC TGCTGATTCT GTAAGCAAAG ATAAAAGCGG CAATATTGTT
1251  CTTTCCGCCA AAGAGGGTGA AGCGGAAATT GGCGGTGTAA TTTCCGCTCA
1301  AAATCAGCAA GCTAAAGGCG GCAAGCTGAT GATTACAGGC GATAAAGTCA
1351  CATTAAAAAC AGGTGCAGTT ATCGACCTTT CAGGTAAAGA AGGGGGAGAA
1401  ACTTACCTTG GCGGTGACGA GCGCGGCGAA GGTAAAAAGG GCATTCAATT
1451  AGCAAAGAAA ACCTCTTTAG AAAAAGGCTC AACCATCAAT GTATCAGGCA
1501  AAGAAAAAGG CGGACGCGCT ATTGTGTGGG GCGATATTGC GTTAATTGAC
```

FIG.1C.

```
1551  GGCAATATTA ACGCTCAAGG TAGTGGTGAT ATCGCTAAAA CCGGTGGTTT
1601  TGTGGAGACG TCGGGGCATG ATTTATTCAT CAAAGACAAT GCAATTGTTG
1651  ACGCCAAAGA GTGGTTGTTA GACCCGGATA ATGTATCTAT TAATGCAGAA
1701  ACAGCAGGAC GCAGCAATAC TTCAGAAGAC GATGAATACA CGGGATCCGG
1751  GAATAGTGCC AGCACCCCAA AACGAAACAA AGAAAAGACA ACATTAACAA
1801  ACACAACTCT TGAGAGTATA CTAAAAAAAG GTACCTTTGT TAACATCACT
1851  GCTAATCAAC GCATCTATGT CAATAGCTCC ATTAATTTAT CCAATGGCAG
1901  CTTAACTCTT TGGAGTGAGG GTCGGAGCGG TGGCGGCGTT GAGATTAACA
1951  ACGATATTAC CACCGGTGAT GATACCAGAG GTGCAAACTT AACAATTTAC
2001  TCAGGCGGCT GGGTTGATGT TCATAAAAAT ATCTCACTCG GGGCGCAAGG
2051  TAACATAAAC ATTACAGCTA AACAAGATAT CGCCTTTGAG AAAGGAAGCA
2101  ACCAAGTCAT TACAGGTCAA GGGACTATTA CCTCAGGCAA TCAAAAAGGT
2151  TTTAGATTTA ATAATGTCTC TCTAAACGGC ACTGGCAGCG GACTGCAATT
2201  CACCACTAAA AGAACCAATA AATACGCTAT CACAAATAAA TTTGAAGGGA
2251  CTTTAAATAT TTCAGGGAAA GTGAACATCT CAATGGTTTT ACCTAAAAAT
2301  GAAAGTGGAT ATGATAAATT CAAAGGACGC ACTTACTGGA ATTTAACCTC
```

FIG.1D.

```
2351  CTTAAATGTT TCCGAGAGTG GCGAGTTTAA CCTCACTATT GACTCCAGAG
2401  GAAGCGATAG TGCAGGCACA CTTACCCAGC CTTATAATTT AAACGGTATA
2451  TCATTCAACA AAGACACTAC CTTTAATGTT GAACGAAATG CAAGAGTCAA
2501  CTTTGACATC AAGGCACCAA TAGGGATAAA TAAGTATTCT AGTTTGAATT
2551  ACGCATCATT TAATGGAAAC ATTTCAGTTT CGGGAGGGGG GAGTGTTGAT
2601  TTCACACTTC TCGCCTCATC CTCTAACGTC CAAACCCCCG GTGTAGTTAT
2651  AAATTCTAAA TACTTTAATG TTTCAACAGG GTCAAGTTTA AGATTTAAAA
2701  CTTCAGGCTC AACAAAAACT GGCTTCTCAA TAGAGAAAGA TTTAACTTTA
2751  AATGCCACCG GAGGCAACAT AACACTTTTG CAAGTTGAAG GCACCGATGG
2801  AATGATTGGT AAAGGCATTG TAGCCAAAAA AAACATAACC TTTGAAGGAG
2851  GTAACATCAC CTTTGGCTCC AGGAAAGCCG TAACAGAAAT CGAAGGCAAT
2901  GTTACTATCA ATAACAACGC TAACGTCACT CTTATCGGTT CGGATTTTGA
2951  CAACCATCAA AAACCTTTAA CTATTAAAAA AGATGTCATC ATTAATAGCG
3001  GCAACCTTAC CGCTGGAGGC AATATTGTCA ATATAGCCGG AAATCTTACC
3051  GTTGAAAGTA ACGCTAATTT CAAAGCTATC ACAAATTTCA CTTTTAATGT
3101  AGGCGGCTTG TTTGACAACA AAGGCAATTC AAATATTTCC ATTGCCAAAG
3151  GAGGGGCTCG CTTTAAAGAC ATTGATAATT CCAAGAATTT AAGCATCACC
```

FIG.1E.

```
3201  ACCAACTCCA GCTCCACTTA CCGCACTATT ATAAGCGGCA ATATAACCAA
3251  TAAAAACGGT GATTTAAATA TTACGAACGA AGGTAGTGAT ACTGAAATGC
3301  AAATTGGCGG CGATGTCTCG CAAAAAGAAG GTAATCTCAC GATTTCTTCT
3351  GACAAAATCA ATATTACCAA ACAGATAACA ATCAAGGCAG GTGTTGATGG
3401  GGAGAATTCC GATTCAGACG CGACAAACAA TGCCAATCTA ACCATTAAAA
3451  CCAAAGAATT GAAATTAACG CAAGACCTAA ATATTTCAGG TTTCAATAAA
3501  GCAGAGATTA CAGCTAAAGA TGGTAGTGAT TTAACTATTG GTAACACCAA
3551  TAGTGCTGAT GGTACTAATG CCAAAAAAGT AACCTTTAAC CAGGTTAAAG
3601  ATTCAAAAAT CTCTGCTGAC GGTCACAAGG TGACACTACA CAGCAAAGTG
3651  GAAACATCCG GTAGTAATAA CAACACTGAA GATAGCAGTG ACAATAATGC
3701  CGGCTTAACT ATCGATGCAA AAAATGTAAC AGTAAACAAC AATATTACTT
3751  CTCACAAAGC AGTGAGCATC TCTGCGACAA GTGGAGAAAT TACCACTAAA
3801  ACAGGTACAA CCATTAACGC AACCACTGGT AACGTGGAGA TAACCGCTCA
3851  AACAGGTAGT ATCCTAGGTG GAATTGAGTC CAGCTCTGGC TCTGTAACAC
3901  TTACTGCAAC CGAGGGCGCT CTTGCTGTAA GCAATATTTC GGGCAACACC
3951  GTTACTGTTA CTGCAAATAG CGGTGCATTA ACCACTTTGG CAGGCTCTAC
```

FIG.1F.

```
4001  AATTAAAGGA ACCGAGAGTG TAACCACTTC AAGTCAATCA GGCGATATCG
4051  GCGGTACGAT TTCTGGTGGC ACAGTAGAGG TTAAAGCAAC CGAAAGTTTA
4101  ACCACTCAAT CCAATTCAAA AATTAAAGCA ACAACAGGCG AGGCTAACGT
4151  AACAAGTGCA ACAGGTACAA TTGGTGGTAC GATTTCCGGT AATACGGTAA
4201  ATGTTACGGC AAACGCTGGC GATTTAACAG TTGGGAATGG CGCAGAAATT
4251  AATGCGACAG AAGGAGCTGC AACCTTAACT ACATCATCGG GCAAATTAAC
4301  TACCGAAGCT AGTTCACACA TTACTTCAGC CAAGGGTCAG GTAAATCTTT
4351  CAGCTCAGGA TGGTAGCGTT GCAGGAAGTA TTAATGCCGC CAATGTGACA
4401  CTAAATACTA CAGGCACTTT AACTACCGTG AAGGGTTCAA ACATTAATGC
4451  AACCAGCGGT ACCTTGGTTA TTAACGCAAA AGACGCTGAG CTAAATGGCG
4501  CAGCATTGGG TAACCACACA GTGGTAAATG CAACCAACGC AAATGGCTCC
4551  GGCAGCGTAA TCGCGACAAC CTCAAGCAGA GTGAACATCA CTGGGGATTT
4601  AATCACAATA AATGGATTAA ATATCATTTC AAAAAACGGT ATAAACACCG
4651  TACTGTTAAA AGGCGTTAAA ATTGATGTGA AATACATTCA ACCGGGTATA
4701  GCAAGCGTAG ATGAAGTAAT TGAAGCGAAA CGCATCCTTG AGAAGGTAAA
4751  AGATTTATCT GATGAAGAAA GAGAAGCGTT AGCTAAACTT GGAGTAAGTG
4801  CTGTACGTTT TATTGAGCCA AATAATACAA TTACAGTCGA TACACAAAAT
```

FIG.1G.

```
4851  GAATTTGCAA CCAGACCATT AAGTCGAATA GTGATTTCTG AAGGCAGGGC
4901  GTGTTTCTCA AACAGTGATG GCGCGACGGT GTGCGTTAAT ATCGCTGATA
4951  ACGGGCGGTA GCGGTCAGTA ATTGACAAGG TAGATTTCAT CCTGCAATGA
5001  AGTCATTTTA TTTTCGTATT ATTTACTGTG TGGGTTAAAG TTCAGTACGG
5051  GCTTTACCCA TCTTGTAAAA AATTACGGAG AATACAATAA AGTATTTTTA
5101  ACAGGTTATT ATTATG
```

FIG. 2A. AMINO ACID SEQUENCE OF HIGH MOLECULAR WEIGHT PROTEIN I

```
  1  MNKIYRLKFS KRLNALVAVS ELARGCDHST EKGSEKPARM KVRHLALKPL
 51  SAMLLSLGVT SIPQSVLASG LQGMDVVHGT ATMQVDGNKT IIRNSVDAII
101  NWKQFNIDQN EMVQFLQENN NSAVFNRVTS NQISQLKGIL DSNGQVFLIN
151  PNGITIGKDA IINTNGFTAS TLDISNENIK ARNFTFEQTK DKALAEIVNH
201  GLITVGKDGS VNLIGGKVKN EGVISVNGGS ISLLAGQKIT ISDIINPTIT
251  YSIAAPENEA VNLGDIFAKG GNINVRAATI RNQGKLSADS VSKDKSGNIV
301  LSAKEGEAEI GGVISAQNQQ AKGGKLMITG DKVTLKTGAV IDLSGKEGGE
351  TYLGGDERGE GKNGIQLAKK TSLEKGSTIN VSGKEKGGRA IVWGDIALID
401  GNINAQGSGD IAKTGGFVET SGHDLFIKDN AIVDAKEWLL DFDNVSINAE
451  TAGRSNTSED DEYTGSGNSA STPKRNKEKT TLTNTTLESI LKKGTFVNIT
501  ANQRIYVNSS INLSNGSLTL WSEGRSGGGV EINNDITTGD DTRGANLTIY
551  SGGWVDVHKN ISLGAQGNIN ITAKQDIAFE KGSNQVITGQ GTITSGNQKG
601  FRFNNVSLNG TGSGLQFTTK RTNKYAITNK FEGTLNISGK VNISMVLPKN
651  ESGYDKFKGR TYWNLTSLNV SESGEFNLTI DSRGSDSAGT LTQPYNLNGI
701  SFNKDTTFNV ERNARVNFDI KAPIGINKYS SLNYASFNGN ISVSGGGSVD
```

FIG.2B.

```
 751  FTLLASSSNV QTPGVVINSK YFNVSTGSSL RFKTSGSTKT GFSIEKDLTL
 801  NATGGNITLL QVEGTDGMIG KGIVAKKNIT FEGGNITFGS RKAVTEIEGN
 851  VTINNNANVT LIGSDFDNHQ KPLTIKKDVI INSGNLTAGG NIVNIAGNLT
 901  VESNANFKAI TNFTFNVGGL FDNKGNSNIS IAKGGARFKD IDNSKNLSIT
 951  TNSSSTYRTI ISGNITNKNG DLNITNEGSD TEMQIGGDVS QKEGNLTISS
1001  DKINITKQIT IKAGVDGENS DSDATNNANL TIKTKELKLT QDLNISGFNK
1051  AEITAKDGSD LTIGNTNSAD GTNAKKVTFN QVKDSKISAD GHKVTLHSKV
1101  ETSGSNNNTE DSSDNNAGLT IDAKNVTVNN NITSHKAVSI SATSGEITTK
1151  TGTTINATTG NVEITAQTGS ILGGIESSSG SVTLTATEGA LAVSNISGNT
1201  VTVTANSGAL TTLAGSTIKG TESVTTSSQS GDIGGTISGG TVEVKATESL
1251  TTQSNSKIKA TTGEANVTSA TGTIGGTISG NTVNVTANAG DLTVGNGAEI
1301  NATEGAATLT TSSGKLTTEA SSHITSAKGQ VNLSAQDGSV AGSINAANVT
1351  LNTTGTLTTV KGSNINATSG TLVINAKDAE LNGAALGNHT VVNATNANGS
1401  GSVIATTSSR VNITGDLITI NGLNIISKNG INTVLLKGVK IDVKYIQPGI
1451  ASVDEVIEAK RILEKVKDLS DEEREALAKL GVSAVRFIEP NNTITVDTQN
1501  EFATRPLSRI VISEGRACFS NSDGATVCVN IADNGR
```

FIG.3A. AMINO ACID SEQUENCE OF HIGH MOLECULAR WEIGHT PROTEIN II (HMW2)

```
  1  TAAATATACA AGATAATAAA AATAAATCAA GATTTTTGTG ATGACAAACA
 51  ACAATTACAA CACCTTTTTT GCAGTCTATA TGCAAATATT TTAAAAAAAT
101  AGTATAAATC CGCCATATAA AATGGTATAA TCTTTCATCT TTCATCTTTA
151  ATCTTTCATC TTTCATCTTT CATCTTTCAT CTTTCATCTT TCATCTTTCA
201  TCTTTCATCT TTCATCTTTC ATCTTTCATC TTTCATCTTT CACATGAAAT
251  GATGAACCGA GGGAAGGGAG GGAGGGGCAA GAATGAAGAG GGAGCTGAAC
301  GAACGCAAAT GATAAAGTAA TTTAATTGTT CAACTAACCT TAGGAGAAAA
351  TATGAACAAG ATATATCGTC TCAAATTCAG CAAACGCCTG AATGCTTTGG
401  TTGCTGTGTC TGAATTGGCA CGGGGTTGTG ACCATTCCAC AGAAAAAGGC
451  TTCCGCTATG TTACTATCTT TAGGTGTAAC CACTTAGCGT TAAAGCCACT
501  TTCCGCTATG TTACTATCTT TAGGTGTAAC ATCTATTCCA CAATCTGTTT
551  TAGCAAGCGG CTTACAAGGA ATGGATGTAG TACACGGCAC AGCCACTATG
601  CAAGTAGATG GTAATAAAAC CATTATCCGC AACAGTGTTG ACGCTATCAT
651  TAATTGGAAA CAATTTAACA TCGACCAAAA TGAAATGGTG CAGTTTTTAC
701  AAGAAAACAA CAACTCCGCC GTATTCAACC GTGTTACATC TAACCAAATC
```

FIG.3B.

```
 751  TCCCAATTAA AAGGGATTTT AGATTCTAAC GGACAAGTCT TTTTAATCAA
 801  CCCAAATGGT ATCACAATAG GTAAAGACGC AATTATTAAC ACTAATGGCT
 851  TTACGGCTTC TACGCTAGAC ATTTCTAACG AAAACATCAA GGCGCGTAAT
 901  TTCACCTTCG AGCAAACCAA AGATAAAGCG CTCGCTGAAA TTGTGAATCA
 951  CGGTTTAATT ACTGTCGGTA AAGACGGCAG TGTAAATCTT ATTGGTGGCA
1001  AAGTGAAAAA CGAGGGTGTG ATTAGCGTAA ATGGTGGCAG CATTTCTTTA
1051  CTCGCAGGGC AAAAAATCAC CATCAGCGAT ATAATAAACC CAACCATTAC
1101  TTACAGCATT GCCGCGCCTG AAAATGAAGC GGTCAATCTG GGCGATATTT
1151  TTGCCAAAGG CGGTAACATT AATGTCCGTG CTGCCACTAT TCGAAACCAA
1201  GGTAAACTTT CTGCTGATTC TGTAAGCAAA GATAAAAGCG GCAATATTGT
1251  TCTTTCCGCC AAAGAGGGTG AAGCGGAAAT TGGCGGTGTA ATTTCCGCTC
1301  AAAATCAGCA AGCTAAAGGC GGCAAGCTGA TGATTACAGG CGATAAAGTC
1351  ACATTAAAAA CAGGTGCAGT TATCGACCTT TCAGGTAAAG AAGGGGGAGA
1401  AACTTACCTT GGCGGTGACG AGCGCGGCGA AGGTAAAAAC GGCATTCAAT
1451  TAGCAAAGAA AACCTCTTTA GAAAAAGGCT CAACCATCAA TGTATCAGGC
1501  AAAGAAAAAG GCGGACGCGC TATTGTGTGG GGCGATATTG CGTTAATTGA
```

FIG.3C.

```
1551  CGGCAATATT AACGCTCAAG GTAGTGGTGA TATCGCTAAA ACCGGTGGTT
1601  TTGTGGAGAC ATCGGGGCAT TATTTATCCA TTGACAGCAA TGCAATTGTT
1651  AAAACAAAAG AGTGGTTGCT AGACCCTGAT GATGTAACAA TTGAAGCCGA
1701  AGACCCCCTT CGCAATAATA CCGGTATAAA TGATGAATTC CCAACAGGCA
1751  CCGGTGAAGC AAGCGACCCT AAAAAAAATA GCGAACTCAA AACAACGCTA
1801  ACCAATACAA CTATTTCAAATTATCTGAAA AACGCCTGGA CAATGAATAT
1851  AACGGCATCA AGAAAACTTA CCGTTAATAG CTCAATCAAC ATCGGAAGCA
1901  ACTCCCACTT AATTCTCCAT AGTAAAGGTC AGCGTGGCGG AGGCGTTCAG
1951  ATTGATGGAG ATATTACTTC TAAAGGCGGA AATTTAACCA TTTATTCTGG
2001  CGGATGGGTT GATGTTCATA AAAATATTAC GCTTGATCAG GGTTTTTTAA
2051  ATATTACCGC CGCTTCCGTA GCTTTTGAAG GTGGAAATAA CAAAGCACGC
2101  GACGCGGCAA ATGCTAAAAT TGTCGCCCAG GGCACTGTAA CCATTACAGG
2151  AGAGGGAAAA GATTTCAGGG CTAACAACGT ATCTTTAAAC GGAACGGGTA
2201  AAGGTCTGAA TATCATTTCA TCAGTGAATA ATTTAACCCA CAATCTTAGT
2251  GGCACAATTA ACATATCTGG GAATATAACA ATTAACCAAA CTACGAGAAA
2301  GAACACCTCG TATTGGCAAA CCAGCCATGA TTCGCACTGG AACGTCAGTG
2351  CTCTTAATCT AGAGACAGGC GCAAATTTTA CCTTTATTAA ATACATTTCA
```

FIG.3D.

```
2401  AGCAATAGCA AAGGCTTAAC AACACAGTAT AGAAGCTCTG CAGGGGTGAA
2451  TTTTAACGGC GTAAATGGCA ACATGTCATT CAATCTCAAA GAAGGAGCGA
2501  AAGTTAATTT CAAATTAAAA CCAAACGAGA ACATGAACAC AAGCAAACCT
2551  TTACCAATTC GGTTTTTAGC CAATATCACA GCCACTGGTG GGGGCTCTGT
2601  TTTTTTTGAT ATATATGCCA ACCATTCTGG CAGAGGGGCT GAGTTAAAAA
2651  TGAGTGAAAT TAATATCTCT AACGGCGCTA ATTTTACCTT AAATTCCCAT
2701  GTTCGCGGCG ATGACGCTTT TAAAATCAAC AAAGACTTAA CCATAAATGC
2751  AACCAATTCA AATTTCAGCC TCAGACAGAC GAAAGATGAT TTTTATGACG
2801  GGTACGCACG CAATGCCATC AATTCAACCT ACAACATATC CATTCTGGGC
2851  GGTAATGTCA CCCTTGGTGG ACAAAACTCA AGCAGCAGCA TTACGGGGAA
2901  TATTACTATC GAGAAAGCAG CAAATGTTAC GCTAGAAGCC AATAACGCCC
2951  CTAATCAGCA AAACATAAGG GATAGAGTTA TAAAACTTGG CAGCTTGCTC
3001  GTTAATGGGA GTTTAAGTTT AACTGGCGAA AATGCAGATA TTAAAGGCAA
3051  TCTCACTATT TCAGAAAGCG CCACTTTTAA AGGAAAGACT AGAGATACCC
3101  TAAATATCAC CGGCAATTTT ACCAATAATG GCACTGCCGA AATTAATATA
3151  ACACAAGGAG TGGTAAAACT TGGCAATGTT ACCAATGATG GTGATTTAAA
```

FIG.3E.

```
3201  CATTACCACT CACGCTAAAC GCAACCAAAG AAGCATCATC GGCGGAGATA
3251  TAATCAACAA AAAAGGAAGC TTAAATATTA CAGACAGTAA TAATGATGCT
3301  GAAATCCAAA TTGGCGGCAA TATCTCGCAA AAAGAAGGCA ACCTCACGAT
3351  TTCTTCCGAT AAAATTAATA TCACCAAACA GATAACAATC AAAAAGGGTA
3401  TTGATGGAGA GGACTCTAGT TCAGATGCGA CAAGTAATGC CAACCTAACT
3451  ATTAAAACCA AAGAATTGAA ATTGACAGAA GACCTAAGTA TTTCAGGTTT
3501  CAATAAAGCA GAGATTACAG CCAAAGATGG TAGAGATTTA ACTATTGGCA
3551  ACAGTAATGA CGGTAACAGC GGTGCCGAAG CCAAAACAGT AACTTTTAAC
3601  AATGTTAAAG ATTCAAAAAT CTCTGCTGAC GGTCACAATG TGACACTAAA
3651  TAGCAAAGTG AAAACATCTA GCAGCAATGG CGGACGTGAA AGCAATAGCG
3701  ACAACGATAC CGGCTTAACT ATTACTGCAA AAAATGTAGA AGTAAACAAA
3751  GATATTACTT CTCTCAAAAC AGTAAATATC ACCGCGTCGG AAAAGGTTAC
3801  CACCACAGCA GGCTCGACCA TTAACGCAAC AAATGGCAAA GCAAGTATTA
3851  CAACCAAAAC AGGTGATATC AGCGGTACGA TTTCCGGTAA CACGGTAAGT
3901  GTTAGCGCGA CTGGTGATTT AACCACTAAA TCCGGCTCAA AAATTGAAGC
3951  GAAATCGGGT GAGGCTAATG TAACAAGTGC AACAGGTACA ATTGGCGGTA
```

FIG.3F.

```
4001  CAATTTCCGG TAATACGGTA AATGTTACGG CAAACGCTGG CGATTTAACA
4051  GTTGGGAATG GCGCAGAAAT TAATGCGACA GAAGGAGCTG CAACCTTAAC
4101  CGCAACAGGG AATACCTTGA CTACTGAAGC CGGTTCTAGC ATCACTTCAA
4151  CTAAGGGTCA GGTAGACCTC TTGGCTCAGA ATGGTAGCAT CGCAGGAAGC
4201  ATTAATGCTG CTAATGTGAC ATTAAATACT ACAGGCACCT TAACCACCGT
4251  GGCAGGCTCG GATATTAAAG CAACCAGCGG CACCTTGGTT ATTAACGCAA
4301  AAGATGCTAA GCTAAATGGT GATGCATCAG GTGATAGTAC AGAAGTGAAT
4351  GCAGTCAACG CAAGCGGCTC TGGTAGTGTG ACTGCGGCAA CCTCAAGCAG
4401  TGTGAATATC ACTGGGGATT TAAACACAGT AAATGGGTTA AATATCATTT
4451  CGAAAGATGG TAGAAACACT GTGCGCTTAA GAGGCAAGGA AATTGAGGTG
4501  AAATATATCC AGCCAGGTGT AGCAAGTGTA GAAGAAGTAA TTGAAGCGAA
4551  ACGCGTCCTT GAAAAAGTAA AAGATTTATC TGATGAAGAA AGAGAAACAT
4601  TAGCTAAACT TGGTGTAAGT GCTGTACGTT TTGTTGAGCC AAATAATACA
4651  ATTACAGTCA ATACACAAAA TGAATTTACA ACCAGACCGT CAAGTCAAGT
4701  GATAATTTCT GAAGGTAAGG CGTGTTTCTC AAGTGGTAAT GGCGCACGAG
4751  TATGTACCAA TGTTGCTGAC GATGGACAGC CGTAGTCAGT AATTGACAAG
4801  GTAGATTTCA TCCTGCAATG AAGTCATTTT ATTTTCGTAT TATTTACTGT
```

FIG.3G.

```
4851  GTGGGTTAAA GTTCAGTACG GGCTTTACCC ATCTTGTAAA AAATTACGGA

4901  GAATACAATA AAGTATTTTT AACAGGTTAT TATTATG
```

FIG.4A. AMINO ACID SEQUENCE OF HIGH MOLECULAR WEIGHT PROTEIN 2

```
  1  MNKIYRLKFS KRLNALVAVS ELARGCDHST EKGSEKPARM KVRHLALKPL
 51  SAMLLSLGVT SIPQSVLASG LQGMDVVHGT ATMQVDGNKT IIRNSVDAII
101  NWKQFNIDQN EMVQFLQENN NSAVFNRVTS NQISQLKGIL DSNGQVFLIN
151  PNGITIGKDA IINTNGFTAS TLDISNENIK ARNFTFEQTK DKALAEIVNH
201  GLITVGKDGS VNLIGGKVKN EGVISVNGGS ISLLAGQKIT ISDIINPTIT
251  YSIAAPENEA VNLGDIFAKG GNINVRAATI RNQGKLSADS VSKDKSGNIV
301  LSAKEGEAEI GGVISAQNQQ AKGGKLMITG DKVTLKTGAV IDLSGKEGGE
351  TYLGGDERGE GKNGIQLAKK TSLEKGSTIN VSGKEKGGRA IVWGDIALID
401  GNINAQGSGD IAKTGGFVET SGHDLFIKDN AIVDAKEWLL DFDNVSINAE
451  DPLRNNTGIN DEFPTGTGEA SDPKKNSELK TTLTNTTISN YLKNAWTMNI
501  TASRKLTVNS SINIGSNSHL ILHSKGQRGG GVQIDGDITS KGGNLTIYSG
551  GWVDVHKNIT LDQGFLNITA ASVAFEGGNN KARDAANAKI VAQGTVTITG
601  EGKDFRANNV SLNGTGKGLN IISSVNNLTH NLSGTINISG NITINQTTRK
651  NTSYWQTSHD SHWNVSALNL ETGANFTFIK YISSNSKGLT TQYRSSAGVN
701  FNGVNGNMSF NLKEGAKVNF KLKPNENMNT SKPLPIRFLA NITATGGGSV
```

FIG.4B.

```
 751  FFDIYANHSG RGAELKMSEI NISNGANFTL NSHVRGDDAF KINKDLTINA
 801  TNSNFSLRQT KDDFYDGYAR NAINSTYNIS ILGGNVTLGG QNSSSSITGN
 851  ITIEKAANVT LEANNAPNQQ NIRDRVIKLG SLLVNGSLSL TGENADIKGN
 901  LTISESATFK GKTRDTLNIT GNFTNNGTAE INITQGVVKL GNVTNDGDLN
 951  ITTHAKRNQR SIIGGDIINK KGSLNITDSN NDAEIQIGGN ISQKEGNLTI
1001  SSDKINITKQ ITIKKGIDGE DSSSDATSNA NLTIKTKELK LTEDLSISGF
1051  NKAEITAKDG RDLTIGNSND GNSGAEAKTV TFNNVKDSKI SADGHNVTLN
1101  SKVKTSSSNG GRESNSDNDT GLTITAKNVE VNKDITSLKT VNITASEKVT
1151  TTAGSTINAT NGKASITTKT GDISGTISGN TVSVSATVDL TTKSGSKIEA
1201  KSGEANVTSA TGTIGGTISG NTVNVTANAG DLTVGNGAEI NATEGAATLT
1251  ATGNTLTTEA GSSITSTKGQ VDLLAQNGSI AGSINAANVT LNTTGTLTTV
1301  AGSDIKATSG TLVINAKDAK LNGDASGDST EVNAVNASGS GSVTAATSSS
1351  VNITGDLNTV NGLNIISKDG RNTVRLRGKE IEVKYIQPGV ASVEEVIEAK
1401  RVLEKVKDLS DEERETLAKL GVSAVRFVEP NNTITVNTQN EFTTRPSSQV
1451  IISEGKACFS SGNGARVCTN VADDGQP
```

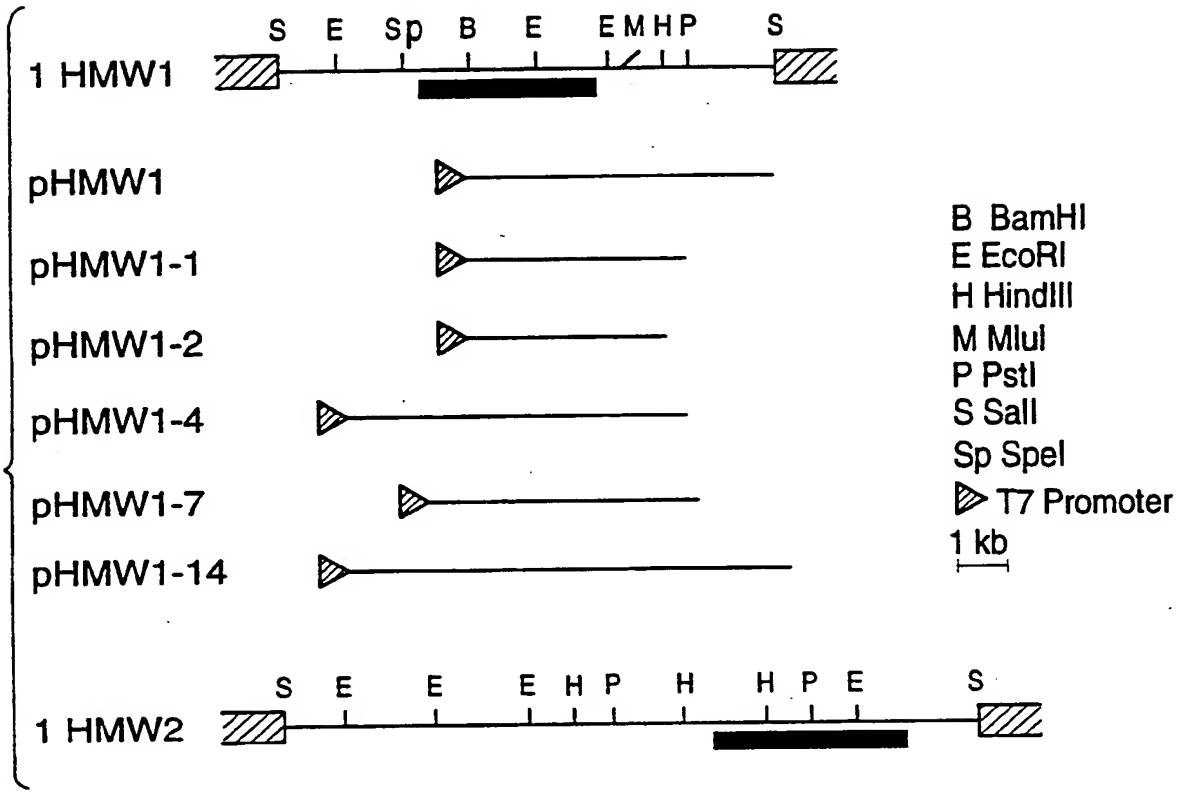
S E Sp B E E M H P S
1 HMW1
pHMW1
pHMW1-1
pHMW1-2
pHMW1-4
pHMW1-7
pHMW1-14
S E E E H P H H P E S
1 HMW2
B BamHI
E EcoRI
H HindIII
M MluI
P PstI
S SalI
Sp SpeI
T7 Promoter
1 kb

FIG.5A.

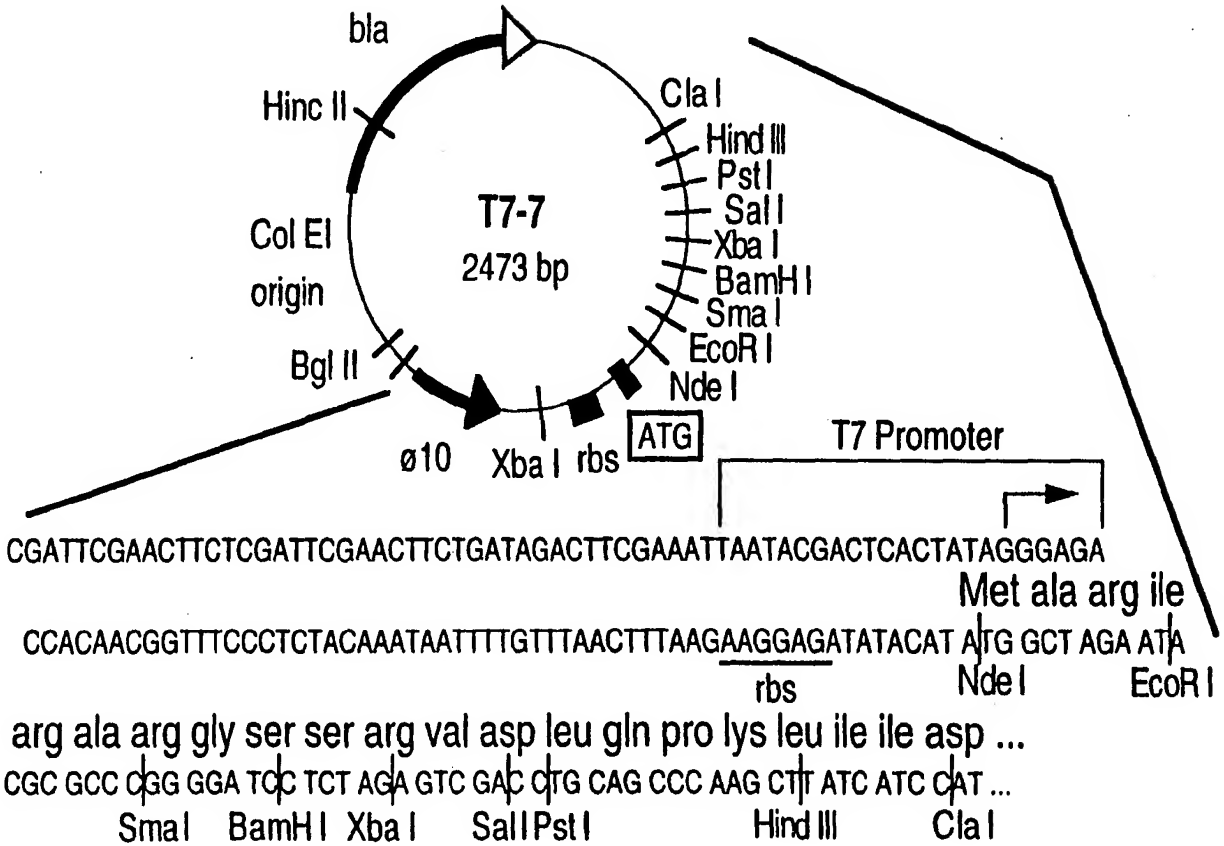

FIG.5B.

(A) Partial restriction maps of representative HMW1 and HMW2 recombinant phage and of HMW1 plasmid subclones. The shaded boxes indicate the locations of the structural genes. In the recombinant phage, transcription proceeds from left to right for the HMW1 gene and from right to left for the HMW2 gene. The methods used for construction of the plasmids shown are described in the text. (B) Restriction map of the T7 expression vector pT7-7. This vector contains the T7 RNA polymerase promoter ϕ10, a ribosome - binding site (rbs), and the translational start site for the T7 gene 10 protein upstream from a multiple cloning site (37).

FIG.6A.

```
  1  ACAGCGTTCT CTTAATACTA GTACAAACCC ACAATAAAAT ATGACAAACA
 51  ACAATTACAA CACCTTTTTT GCAGTCTATA TGCAAATATT TTAAAAAATA
101  GTATAAATCC GCCATATAAA ATGGTATAAT CTTTCATCTT TCATCTTTCA
151  TCTTTCATCT TTCATCTTTC ATCTTTCATC TTTCATCTTT CATCTTTCAT
201  CTTTCATCTT TCATCTTTCA TCTTTCATCT TTCATCTTTC ACATGAAATG
251  ATGAACCGAG GGAAGGGAGG GAGGGGCAAG AATGAAGAGG GAGCTGAACG
301  AACGCAAATG ATAAAGTAAT TTAATTGTTC AACTAACCTT AGGAGAAAAT
351  ATGAACAAGA TATATCGTCT CAAATTCAGC AAACGCCTGA ATGCTTTGGT
401  TGCTGTGTCT GAATTGGCAC GGGGTTGTGA CCATTCCACA GAAAAAGGCA
451  GCGAAAAACC TGCTCGCATG AAAGTGCGTC ACTTAGCGTT AAAGCCACTT
501  TCCGCTATGT TACTATCTTT AGGTGTAACA TCTATTCCAC AATCTGTTTT
551  AGCAAGCGGC TTACAAGGAA TGGATGTAGT ACACGGCACA GCCACTATGC
601  AAGTAGATGG TAATAAAACC ATTATCCGCA ACAGTGTTGA CGCTATCATT
651  AATTGGAAAC AATTTAACAT CGACCAAAAT GAAATGGTGC AGTTTTTACA
701  AGAAAACAAC AACTCCGCCG TATTCAACCG TGTTACATCT AACCAAATCT
751  CCCAATTAAA AGGGATTTTA GATTCTAACG GACAAGTCTT TTTAATCAAC
```

FIG.6B.

```
 801  CCAAATGGTA TCACAATAGG TAAAGACGCA ATTATTAACA CTAATGGCTT
 851  TACGGCTTCT ACGCTAGACA TTTCTAACGA AAACATCAAG GCGCGTAATT
 901  TCACCTTCGA GCAAACCAAA GATAAAGCGC TCGCTGAAAT TGTGAATCAC
 951  GGTTTAATTA CTGTCGGTAA AGACGGCAGT GTAAATCTTA TTGGTGGCAA
1001  AGTGAAAAAC GAGGGTGTGA TTAGCGTAAA TGGTGGCAGC ATTTCTTTAC
1051  TCGCAGGGCA AAAAATCACC ATCAGCGATA TAATAAACCC AACCATTACT
1101  TACAGCATTG CCGCGCCTGA AAATGAAGCG GTCAATCTGG GCGATATTTT
1151  TGCCAAAGGC GGTAACATTA ATGTCCGTGC TGCCACTATT CGAAACCAAG
1251  CTTTCCGCCA AAGAGGGTGA AGCGGAAATT GGCGGTGTAA TTTCCGCTCA
1301  AAATCAGCAA GCTAAAGGCG GCAAGCTGAT GATTACAGGC GATAAAGTCA
1351  CATTAAAAAC AGGTGCAGTT ATCGACCTTT CAGGTAAAGA AGGGGGAGAA
1401  ACTTACCTTG GCGGTGACGA GCGCGGCGAA GGTAAAAACG GCATTCAATT
1451  AGCAAAGAAA ACCTCTTTAG AAAAAGGCTC AACCATCAAT GTATCAGGCA
1501  AAGAAAAAGG CGGACGCGCT ATTGTGTGGG GCGATATTGC GTTAATTGAC
1551  GGCAATATTA ACGCTCAAGG TAGTGGTGAT ATCGCTAAAA CCGGTGGTTT
1601  TGTGGAGACG TCGGGGCATG ATTTATTCAT CAAAGACAAT GCAATTGTTG
```

FIG.6C.

```
1651  ACGCCAAAGA GTGGTTGTTA GACCCGGATA ATGTATCTAT TAATGCAGAA
1701  ACAGCAGGAC GCAGCAATAC TTCAGAAGAC GATGAATACA CGGGATCCGG
1751  GAATAGTGCC AGCACCCCAA AACGAAACAA AGAAAAGACA ACATTAACAA
1801  ACACAACTCT TGAGAGTATA CTAAAAAAAG GTACCTTTGT TAACATCACT
1851  GCTAATCAAC GCATCTATGT CAATAGCTCC ATTAATTTAT CCAATGGCAG
1901  CTTAACTCTT TGGAGTGAGG GTCGGAGCGG TGGCGGCGTT GAGATTAACA
1951  ACGATATTAC CACCGGTGAT GATACCAGAG GTGCAAACTT AACAATTTAC
2001  TCAGGCGGCT GGGTTGATGT TCATAAAAAT ATCTCACTCG GGGCGCAAGG
2051  TAACATAAAC ATTACAGCTA AACAAGATAT CGCCTTTGAG AAAGGAAGCA
2101  ACCAAGTCAT TACAGGTCAA GGGACTATTA CCTCAGGCAA TCAAAAAGGT
2151  TTTAGATTTA ATAATGTCTC TCTAAACGGC ACTGGCAGCG GACTGCAATT
2201  CACCACTAAA AGAACCAATA AATACGCTAT CACAAATAAA TTTGAAGGGA
2251  CTTTAAATAT TTCAGGGAAA GTGAACATCT CAATGGTTTT ACCTAAAAAT
2301  GAAAGTGGAT ATGATAAATT CAAAGGACGC ACTTACTGGA ATTTAACCTC
2351  GAAAGTGGAT ATGATAAATT CAAAGGACGC CCTCACTATT GACTCCAGAG
2401  GAAGCGATAG TGCAGGCACA CTTACCCAGC CTTATAATTT AAACGGTATA
2451  TCATTCAACA AAGACACTAC CTTTAATGTT GAACGAAATG CAAGAGTCAA
```

FIG.6D.

```
2501  CTTTGACATC AAGGCACCAA TAGGGATAAA TAAGTATTCT AGTTTGAATT
2551  ACGCATCATT TAATGGAAAC ATTTCAGTTT CGGGAGGGGG GAGTGTTGAT
2601  TTCACACTTC TCGCCTCATC CTCTAACGTC CAAACCCCCG GTGTAGTTAT
2651  AAATTCTAAA TACTTTAATG TTTCAACAGG GTCAAGTTTA AGATTTAAAA
2701  CTTCAGGCTC AACAAAAACT GGCTTCTCAA TAGAGAAAGA TTTAACTTTA
2751  AATGCCACCG GAGGCAACAT AACACTTTTG CAAGTTGAAG GCACCGATGG
2801  AATGATTGGT AAAGGCATTG TAGCCAAAAA AAACATAACC TTTGAAGGAG
2851  GTAAGATGAG GTTTGGCTCC AGGAAAGCCG TAACAGAAAT CGAAGGCAAT
2901  GTTACTATCA ATAACAACGC TAACGTCACT CTTATCGGTT CGGATTTTGA
2951  CAACCATCAA AAACCTTTAA CTATTAAAAA AGATGTCATC ATTAATAGCG
3001  GCAACCTTAC CGCTGGAGGC AATATTGTCA ATATAGCCGG AAATCTTACC
3051  GTTGAAAGTA ACGCTAATTT CAAAGCTATC ACAAATTTCA CTTTTAATGT
3101  AGGCGGCTTG TTTGACAACA AAGGCAATTC AAATATTTCC ATTGCCAAAG
3151  GAGGGGCTCG CTTTAAAGAC ATTGATAATT CCAAGAATTT AAGCATCACC
3201  ACCAACTCCA GCTCCACTTA CCGCACTATT ATAAGCGGCA ATATAACCAA
3251  TAAAAACGGT GATTTAAATA TTACGAACGA AGGTAGTGAT ACTGAAATGC
```

FIG.6E.

```
3301  AAATTGGCGG CGATGTCTCG CAAAAAGAAG GTAATCTCAC GATTTCTTCT
3351  GACAAAATCA ATATTACCAA ACAGATAACA ATCAAGGCAG GTGTTGATGG
3401  GGAGAATTCC GATTCAGACG CGACAAACAA TGCCAATCTA ACCATTAAAA
3451  CCAAAGAATT GAAATTAACG CAAGACCTAA ATATTTCAGG TTTCAATAAA
3501  GCAGAGATTA CAGCTAAAGA TGGTAGTGAT TTAACTATTG GTAACACCAA
3551  TAGTGCTGAT GGTACTAATG CCAAAAAAGT AACCTTTAAC CAGGTTAAAG
3601  ATTCAAAAAT CTCTGCTGAC GGTCACAAGG TGACACTACA CAGCAAAGTG
3651  GAAACATCCG GTAGTAATAA CAACACTGAA GATAGCAGTG ACAATAATGC
3701  CGGCTTAACT ATCGATGCAA AAAATGTAAC AGTAAACAAC AATATTACTT
3751  CTCACAAAGC AGTGAGCATC TCTGCGACAA GTGGAGAAAT TACCACTAAA
3801  ACAGGTACAA CCATTAACGC AACCACTGGT AACGTGGAGA TAACCGCTCA
3851  AACAGGTAGT ATCCTAGGTG GAATTGAGTC CAGCTCTGGC TCTGTAACAC
3901  TTACTGCAAC CGAGGGCGCT CTTGCTGTAA GCAATATTTC GGGCAACACC
3951  GTTACTGTTA CTGCAAATAG CGGTGCATTA ACCACTTTGG CAGGCTCTAC
4001  AATTAAAGGA ACCGAGAGTG TAACCACTTC AAGTCAATCA GGCGATATCG
4051  GCGGTACGAT TTCTGGTGGC ACAGTAGAGG TTAAAGCAAC CGAAAGTTTA
```

FIG.6F.

```
4101  ACCACTCAAT CCAATTCAAA AATTAAAGCA ACAACAGGCG AGGCTAACGT
4151  AACAAGTGCA ACAGGTACAA TTGGTGGTAC GATTTCCGGT AATACGGTAA
4201  ATGTTACGGC AAACGCTGGC GATTTAACAG TTGGGAATGG CGCAGAAATT
4251  AATGCGACAG AAGGAGCTGC AACCTTAACT ACATCATCGG GCAAATTAAC
4301  TACCGAAGCT AGTTCACACA TTACTTCAGC CAAGGGTCAG GTAAATCTTT
4351  CAGCTCAGGA TGGTAGCGTT GCAGGAAGTA TTAATGCCGC CAATGTGACA
4401  CTAAATACTA CAGGCACTTT AACTACCGTG AAGGGTTCAA ACATTAATGC
4451  AACCAGCGGT ACCTTGGTTA TTAACGCAAA AGACGCTGAG CTAAATGGCG
4501  CAGCATTGGG TAACCACACA GTGGTAAATG CAACCAACGC AAATGGCTCC
4551  GGCAGCGTAA TCGCGACAAC CTCAAGCAGA GTGAACATCA CTGGGGATTT
4601  AATCACAATA AATGGATTAA ATATCATTTC AAAAAACGGT ATAAACACCG
4651  TACTGTTAAA AGGCGTTAAA ATTGATGTGA AATACATTCA ACCGGGTATA
4701  GCAAGCGTAG ATGAAGTAAT TGAAGCGAAA CGCATCCTTG AGAAGGTAAA
4751  AGATTTATCT GATGAAGAAA GAGAAGCGTT AGCTAAACTT GGCGTAAGTG
4801  CTGTACGTTT TATTGAGCCA AATAATACAA TTACAGTCGA TACACAAAAT
4851  GAATTTGCAA CCAGACCATT AAGTCGAATA GTGATTTCTG AAGGCAGGGC
4901  GTGTTTCTCA AACAGTGATG GCGCGACGGT GTGCGTTAAT ATCGCTGATA
```

FIG.6G.

```
4951  ACGGGCGGTA GCGGTCAGTA ATTGACAAGG TAGATTTCAT CCTGCAATGA
5001  AGTCATTTTA TTTTCGTATT ATTTACTGTG TGGGTTAAAG TTCAGTACGG
5051  GCTTTACCCA TCTTGTAAAA AATTACGGAG AATACAATAA AGTATTTTTA
5101  ACAGGTTATT ATTATGAAAA ATATAAAAAG CAGATTAAAA CTCAGTGCAA
5151  TATCAGTATT GCTTGGCCTG GCTTCTTCAT CATTGTATGC AGAAGAAGCG
5201  TTTTTAGTAA AAGGCTTTCA GTTATCTGGT GCACTTGAAA CTTTAAGTGA
5251  AGACGCCCAA CTGTCTGTAG CAAAATCTTT ATCTAAATAC CAAGGCTCGC
5301  AAACTTTAAC AAACCTAAAA ACAGCACAGC TTGAATTACA GGCTGTGCTA
5351  GATAAGATTG AGCCAAATAA GTTTGATGTG ATATTGCCAC AACAAACCAT
5401  TACGGATGGC AATATTATGT TTGAGCTAGT CTCGAAATCA GCCGCAGAAA
5451  GCCAAGTTTT TTATAAGGCG AGCCAGGGTT ATAGTGAAGA AAATATCGCT
5501  CGTAGCCTGC CATCTTTGAA ACAAGGAAAA GTGTATGAAG ATGGTCGTCA
5551  GTGGTTCGAT TTGCGTGAAT TCAATATGGC AAAAGAAAAT CCACTTAAAG
5601  TCACTCGCGT GCATTACGAG TTAAACCCTA AAAACAAAAC CTCTGATTTG
5651  GTAGTTGCAG GTTTTTCGCC TTTTGGCAAA ACGCGTAGCT TTGTTTCCTA
5701  TGATAATTTC GGCGCAAGGG AGTTTAACTA TCAACGTGTA AGTCTAGGTT
```

FIG.6H.

```
5751  TTGTAAATGC CAATTTGACC GGACATGATG ATGTATTAAA TCTAAACGCA
5801  TTGACCAATG TAAAAGCACC ATCAAAATCT TATGCGGTAG GCATAGGATA
5851  TACTTATCCG TTTTATGATA AACACCAATC CTTAAGTCTT TATACCAGCA
5901  TGAGTTATGC TGATTCTAAT GATATCGACG GCTTACCAAG TGCGATTAAT
5951  CGTAAATTAT CAAAAGGTCA ATCTATCTCT GCGAATCTGA AATGGAGTTA
6001  TTATCTCCCG ACATTTAACC TTGGAATGGA AGACCAGTTT AAAATTAATT
6051  TAGGCTACAA CTACCGCCAT ATTAATCAAA CATCCGAGTT AAACACCCTG
6101  GGTGCAACGA AGAAAAAATT TGCAGTATCA GGCGTAAGTG CAGGCATTGA
6151  TGGACATATC CAATTTACCC CTAAAACAAT CTTTAATATT GATTTAACTC
6201  ATCATTATTA CGCGAGTAAA TTACCAGGCT CTTTTGGAAT GGAGCGCATT
6251  GGCGAAACAT TTAATCGCAG CTATCACATT AGCACAGCCA GTTTAGGGTT
6301  GAGTCAAGAG TTTGCTCAAG GTTGGCATTT TAGCAGTCAA TTATCGGGTC
6351  AGTTTACTCT ACAAGATATA AGTAGCATAG ATTTATTCTC TGTAACAGGT
6401  ACTTATGGCG TCAGAGGCTT TAAATACGGC GGTGCAAGTG GTGAGCGCGG
6451  TCTTGTATGG CGTAATGAAT TAAGTATGCC AAAATACACC CGCTTTCAAA
6501  TCAGCCCTTA TGCGTTTTAT GATGCAGGTC AGTTCCGTTA TAATAGCGAA
6551  AATGCTAAAA CTTACGGCGA AGATATGCAC ACGGTATCCT CTGCGGGTTT
```

FIG.6I.

```
6601  AGGCATTAAA ACCTCTCCTA CACAAAACTT AAGCTTAGAT GCTTTTGTTG
6651  CTCGTCGCTT TGCAAATGCC AATAGTGACA ATTTGAATGG CAACAAAAAA
6701  CGCACAAGCT CACCTACAAC CTTCTGGGGT AGATTAACAT TCAGTTTCTA
6751  ACCCTGAAAT TTAATCAACT GGTAAGCGTT CCGCCTACCA GTTTATAACT
6801  ATATGCTTTA CCCGCCAATT TACAGTCTAT ACGCAACCCT GTTTTCATCC
6851  TTATATATCA AACAAACTAA GCAAACCAAG CAAACCAAGC AAACCAAGCA
6901  AACCAAGCAA ACCAAGCAAA CCAAGCAAAC CAAGCAAACC AAGCAAACCA
6951  AGCAAACCAA GCAAACCAAG CAAACCAAGC AAACCAAGCA ATGCTAAAAA
7001  ACAATTTATA TGATAAACTA AAACATACTC CATACCATGG CAATACAAGG
7051  GATTTAATAA TATGACAAAA GAAAATTTAC AAAGTGTTCC ACAAAATACG
7101  ACCGCTTCAC TTGTAGAATC AAACAACGAC CAAACTTCCC TGCAAATACT
7151  TAAACAACCA CCCAAACCCA ACCTATTACG CCTGGAACAA CATGTCGCCA
7201  AAAAAGATTA TGAGCTTGCT TGCCGCGAAT TAATGGCGAT TTTGGAAAAA
7251  ATGGACGCTA ATTTTGGAGG CGTTCACGAT ATTGAATTTG ACGCACCTGC
7301  TCAGCTGGCA TATCTACCCG AAAAACTACT AATTCATTTT GCCACTCGTC
7351  TCGCTAATGC AATTACAACA CTCTTTTCCG ACCCCGAATT GGCAATTTCC
```

FIG.6J.

```
7401  GAAGAAGGGG CATTAAAGAT GATTAGCCTG CAACGCTGGT TGACGCTGAT
7451  TTTTGCCTCT TCCCCCTACG TTAACGCAGA CCATATTCTC AATAAATATA
7501  ATATCAACCC AGATTCCGAA GGTGGCTTTC ATTTAGCAAC AGACAACTCT
7551  TCTATTGCTA AATTCTGTAT TTTTTACTTA CCCGAATCCA ATGTCAATAT
7601  GAGTTTAGAT GCGTTATGGG CAGGGAATCA ACAACTTTGT GCTTCATTGT
7651  GTTTTGCGTT GCAGTCTTCA CGTTTTATTG GTACTGCATC TGCGTTTCAT
7701  AAAAGAGCGG TGGTTTTACA GTGGTTTCCT AAAAAACTCG CCGAAATTGC
7751  TAATTTAGAT GAATTGCCTG CAAATATCCT TCATGATGTA TATATGCACT
7801  GCAGTTATGA TTTAGCAAAA AACAAGCACG ATGTTAAGCG TCCATTAAAC
7851  GAACTTGTCC GCAAGCATAT CCTCACGCAA GGATGGCAAG ACCGCTACCT
7901  TTACACCTTA GGTAAAAAGG ACGGCAAACC TGTGATGATG GTACTGCTTG
7951  AACATTTTAA TTCGGGACAT TCGATTTATC GCACGCATTC AACTTCAATG
8001  ATTGCTGCTC GAGAAAAATT CTATTTAGTC GGCTTAGGCC ATGAGGGCGT
8051  TGATAACATA GGTCGAGAAG TGTTTGACGA GTTCTTTGAA ATCAGTAGCA
8101  ATAATATAAT GGAGAGACTG TTTTTTATCC GTAAACAGTG CGAAACTTTC
8151  CAACCCGCAG TGTTCTATAT GCCAAGCATT GGCATGGATA TTACCACGAT
```

FIG.6K.

```
8201  TTTTGTGAGC AACACTCGGC TTGCCCCTAT TCAAGCTGTA GCCTTGGGTC
8251  ATCCTGCCAC TACGCATTCT GAATTTATTG ATTATGTCAT CGTAGAAGAT
8301  GATTATGTGG GCAGTGAAGA TTGTTTAGC  GAAACCCTTT TACGCTTACC
8351  CAAAGATGCC CTACCTTATG TACCATCTGC ACTCGCCCCA CAAAAAGTGG
8401  ATTATGTACT CAGGGAAAAC CCTGAAGTAG TCAATATCGG TATTGCCGCT
8451  ACCACAATGA AATTAAACCC TGAATTTTTG CTAACATTGC AAGAAATCAG
8501  AGATAAAGCT AAAGTCAAAA TACATTTTCA TTTCGCACTT GGACAATCAA
8551  CAGGCTTGAC ACACCCTTAT GTCAAATGGT TTATCGAAAG CTATTTAGGT
8601  GACGATGCCA CTGCACATCC CCACGCACCT TATCACGATT ATCTGGCAAT
8651  ATTGCGTGAT TGCGATATGC TACTAAATCC GTTTCCTTTC GGTAATACTA
8701  ACGGCATAAT TGATATGGTT ACATTAGGTT TAGTTGGTGT ATGCAAAACG
8751  GGGGATGAAG TACATGAACA TATTGATGAA GGTCTGTTTA AACGCTTAGG
8801  ACTACCAGAA TGGCTGATAG CCGACACACG AGAAACATAT ATTGAATGTG
8851  CTTTGCGTCT AGCAGAAAAC CATCAAGAAC GCCTTGAACT CCGTCGTTAC
8901  ATCATAGAAA ACAACGGCTT ACAAAAGCTT TTTACAGGCG ACCCTCGTCC
8951  ATTGGGCAAA ATACTGCTTA AGAAAACAAA TGAATGGAAG CGGAAGCACT
9001  TGAGTAAAAA ATAACGGTTT TTTAAAGTAA AAGTGCGGTT AATTTTCAAA
```

FIG.6L.

```
9051  GCGTTTTAAA AACCTCTCAA AAATCAACCG CACTTTTATC TTTATAACGC
9101  TCCCGCGCGC TGACAGTTTA TCTCTTTCTT AAAATACCCA TAAAATTGTG
9151  GCAATAGTTG GGTAATCAAA TTCAATTGTT GATACGGCAA ACTAAAGACG
9201  GCGCGTTCTT CGGCAGTCAT C
```

FIG.7A.

```
  1  CGCCACTTCA ATTTTGGATT GTTGAAATTC AACTAACCAA AAAGTGCGGT
 51  TAAAATCTGT GGAGAAAATA GGTTGTAGTG AAGAACGAGG TAATTGTTCA
101  AAAGGATAAA GCTCTCTTAA TTGGGCATTG GTTGGCGTTT CTTTTTCGGT
151  TAATAGTAAA TTATATTCTG GACGACTATG CAATCCACCA ACAACTTTAC
201  CGTTGGTTTT AAGCGTTAAT GTAAGTTCTT GCTCTTCTTG GCGAATACGT
251  AATCCCATTT TTTGTTTAGC AAGAAAATGA TCGGGATAAT CATAATAGGT
301  GTTGCCCAAA AATAAATTTT GATGTTCTAA AATCATAAAT TTTGCAAGAT
351  ATTGTGGCAA TTCAATACCT ATTTGTGGCG AAATCGCCAA TTTTAATTCA
401  ATTTCTTGTA GCATAATATT TCCCACTCAA ATCAACTGGT TAAATATACA
451  AGATAATAAA AATAAATCAA GATTTTTGTG ATGACAAACA ACAATTACAA
501  CACCTTTTTT GCAGTCTATA TGCAAATATT TTAAAAAAAT AGTATAAATC
551  CGCCATATAA AATGGTATAA TCTTTCATCT TTCATCTTTC ATCTTTCATC
601  TTTCATCTTT CATCTTTCAT CTTTCATCTT TCATCTTTCA TCTTTCATCT
651  TTCATCTTTC ATCTTTCATC TTTCATCTTT CACATGAAAT GATGAACCGA
701  GGGAAGGGAG GGAGGGGCAA GAATGAAGAG GGAGCTGAAC GAACGCAAAT
751  GATAAAGTAA TTTAATTGTT CAACTAACCT TAGGAGAAAA TATGAACAAG
```

FIG.7B.

```
 801  ATATATCGTC TCAAATTCAG CAAACGCCTG AATGCTTTGG TTGCTGTGTC
 851  TGAATTGGCA CGGGGTTGTG ACCATTCCAC AGAAAAAGGC AGCGAAAAAC
 901  CTGCTCGCAT GAAAGTGCGT CACTTAGCGT TAAAGCCACT TTCCGCTATG
 951  TTACTATCTT TAGGTGTAAC ATCTATTCCA CAATCTGTTT TAGCAAGCGG
1001  CAATTTAACA TCGACCAAAA TGAAATGGTG CAGTTTTTAC AAGAAAACAA
1051  GTAATAAAAC CATTATCCGC AACAGTGTTG ACGCTATCAT TAATTGGAAA
1101  CAATTTAACA TCGACCAAAA TGAAATGGTG CAGTTTTTAC AAGAAAACAA
1151  CAACTCCGCC GTATTCAACC GTGTTACATC TAACCAAATC TCCCAATTAA
1201  AAGGGATTTT AGATTCTAAC GGACAAGTCT TTTTAATCAA CCCAAATGGT
1251  ATCACAATAG GTAAAGACGC AATTATTAAC ACTAATGGCT TTACGGCTTC
1301  TACGCTAGAC ATTTCTAACG AAAACATCAA GGCGCGTAAT TTCACCTTCG
1351  AGCAAACCAA AGATAAAGCG CTCGCTGAAA TTGTGAATCA CGGTTTAATT
1401  ACTGTCGGTA AAGACGGCAG TGTAAATCTT ATTGGTGGCA AAGTGAAAAA
1451  CGAGGGTGTG ATTAGCGTAA ATGGTGGCAG CATTTCTTTA CTCGCAGGGC
1501  AAAAAATCAC CATCAGCGAT ATAATAAACC CAACCATTAC TTACAGCATT
1551  GCCGCGCCTG AAAATGAAGC GGTCAATCTG GGCGATATTT TTGCCAAAGG
```

FIG.7C.

```
1601  CGGTAACATT AATGTCCGTG CTGCCACTAT TCGAAACCAA GGTAAACTTT
1651  CTGCTGATTC TGTAAGCAAA GATAAAAGCG GCAATATTGT TCTTTCCGCC
1701  AAAGAGGGTG AAGCGGAAAT TGGCGGTGTA ATTTCCGCTC AAAATCAGCA
1751  AGCTAAAGGC GGCAAGCTGA TGATTACAGG CGATAAAGTC ACATTAAAAA
1801  CAGGTGCAGT TATCGACCTT TCAGGTAAAG AAGGGGGAGA AACTTACCTT
1851  GGCGGTGACG AGCGCGGCGA AGGTAAAAAC GGCATTCAAT TAGCAAAGAA
1901  AACCTCTTTA GAAAAAGGCT CAACCATCAA TGTATCAGGC AAAGAAAAAG
1951  GCGGACGCGC TATTGTGTGG GGCGATATTG CGTTAATTGA CGGCAATATT
2001  AACGCTCAAG GTAGTGGTGA TATCGCTAAA ACCGGTGGTT TTGTGGAGAC
2051  ATCGGGGCAT TATTTATCCA TTGACAGCAA TGCAATTGTT AAAACAAAAG
2101  AGTGGTTGCT AGACCCTGAT GATGTAACAA TTGAAGCCGA AGACCCCCTT
2151  CGCAATAATA CCGGTATAAA TGATGAATTC CCAACAGGCA CCGGTGAAGC
2201  AAGCGACCCT AAAAAAAATA GCGAACTCAA AACAACGCTA ACCAATACAA
2251  CTATTTCAAA TTATCTGAAA AACGCCTGGA CAATGAATAT AACGGCATCA
2301  AGAAAACTTA CCGTTAATAG CTCAATCAAC ATCGGAAGCA ACTCCCACTT
2351  AATTCTCCAT AGTAAAGGTC AGCGTGGCGG AGGCGTTCAG ATTGATGGAG
2401  ATATTACTTC TAAAGGCGGA AATTTAACCA TTTATTCTGG CGGATGGGTT
```

FIG.7D.

```
2451  GATGTTCATA AAAATATTAC GCTTGATCAG GGTTTTTTAA ATATTACCGC
2501  CGCTTCCGTA GCTTTTGAAG GTGGAAATAA CAAAGCACGC GACGCGGCAA
2551  ATGCTAAAAT TGTCGCCCAG GGCACTGTAA CCATTACAGG AGAGGGAAAA
2601  GATTTCAGGG CTAACAACGT ATCTTTAAAC GGAACGGGTA AAGGTCTGAA
2651  TATCATTTCA TCAGTGAATA ATTTAACCCA CAATCTTAGT GGCACAATTA
2701  ACATATCTGG GAATATAACA ATTAACCAAA CTACGAGAAA GAACACCTCG
2751  TATTGGCAAA CCAGCCATGA TTCGCACTGG AACGTCAGTG CTCTTAATCT
2801  AGAGACAGGC GCAAATTTTA CCTTTATTAA ATACATTTCA AGCAATAGCA
2851  AAGGCTTAAC AACACAGTAT AGAAGCTCTG CAGGGGTGAA TTTTAACGGC
2901  GTAAATGGCA ACATGTCATT CAATCTCAAA GAAGGAGCGA AAGTTAATTT
2951  CAAATTAAAA CCAAACGAGA ACATGAACAC AAGCAAACCT TTACCAATTC
3001  GGTTTTTAGC CAATATCACA GCCACTGGTG GGGGCTCTGT TTTTTTTGAT
3051  ATATATGCCA ACCATTCTGG CAGAGGGGCT GAGTTAAAAA TGAGTGAAAT
3101  TAATATCTCT AACGGCGCTA ATTTTACCTT AAATTCCCAT GTTCGCGGCG
3151  ATGACGCTTT TAAAATCAAC AAAGACTTAA CCATAAATGC AACCAATTCA
3201  AATTTCAGCC TCAGACAGAC GAAAGATGAT TTTTATGACG GGTACGCACG
```

FIG.7E.

```
3251  CAATGCCATC AATTCAACCT ACAACATATC CATTCTGGGC GGTAATGTCA
3301  CCCTTGGTGG ACAAAACTCA AGCAGCAGCA TTACGGGGAA TATTACTATC
3351  GAGAAAGCAG CAAATGTTAC GCTAGAAGCC AATAACGCCC CTAATCAGCA
3401  AAACATAAGG GATAGAGTTA TAAAACTTGG CAGCTTGCTC GTTAATGGGA
3451  GTTTAAGTTT AACTGGCGAA AATGCAGATA TTAAAGGCAA TCTCACTATT
3501  TCAGAAAGCG CCACTTTTAA AGGAAAGACT AGAGATACCC TAAATATCAC
3551  CGGCAATTTT ACCAATAATG GCACTGCCGA AATTAATATA ACACAAGGAG
3601  TGGTAAAACT TGGCAATGTT ACCAATGATG GTGATTTAAA CATTACCACT
3651  CACGCTAAAC GCAACCAAAG AAGCATCATC GGCGGAGATA TAATCAACAA
3701  AAAAGGAAGC TTAAATATTA CAGACAGTAA TAATGATGCT GAAATCCAAA
3751  TTGGCGGCAA TATCTCGCAA AAAGAAGGCA ACCTCACGAT TTCTTCCGAT
3801  AAAATTAATA TCACCAAACA GATAACAATC AAAAAGGGTA TTGATGGAGA
3851  GGACTCTAGT TCAGATGCGA CAAGTAATGC CAACCTAACT ATTAAAACCA
3901  AAGAATTGAA ATTGACAGAA GACCTAAGTA TTTCAGGTTT CAATAAAGCA
3951  GAGATTACAG CCAAAGATGG TAGAGATTTA ACTATTGGCA ACAGTAATGA
4001  CGGTAACAGC GGTGCCGAAG CCAAAACAGT AACTTTTAAC AATGTTAAAG
```

FIG.7F.

```
4051  ATTCAAAAAT CTCTGCTGAC GGTCACAATG TGACACTAAA TAGCAAAGTG
4101  AAAACATCTA GCAGCAATGG CGGACGTGAA AGCAATAGCG ACAACGATAC
4151  CGGCTTAACT ATTACTGCAA AAAATGTAGA AGTAAACAAA GATATTACTT
4201  CTCTCAAAAC AGTAAATATC ACCGCGTCGG AAAAGGTTAC CACCACAGCA
4251  GGCTCGACCA TTAACGCAAC AAATGGCAAA GCAAGTATTA CAACCAAAAC
4301  AGGTGATATC AGCGGTACGA TTTCCGGTAA CACGGTAAGT GTTAGCGCGA
4351  CTGGTGATTT AACCACTAAA TCCGGCTCAA AAATTGAAGC GAAATCGGGT
4401  GAGGCTAATG TAACAAGTGC AACAGGTACA ATTGGCGGTA CAATTTCCGG
4451  TAATACGGTA AATGTTACGG CAAACGCTGG CGATTTAACA GTTGGGAATG
4501  GCGCAGAAAT TAATGCGACA GAAGGAGCTG CAACCTTAAC CGCAACAGGG
4551  AATACCTTGA CTACTGAAGC CGGTTCTAGC ATCACTTCAA CTAAGGGTCA
4601  GGTAGACCTC TTGGCTCAGA ATGGTAGCAT CGCAGGAAGC ATTAATGCTG
4651  CTAATGTGAC ATTAAATACT ACAGGCACCT TAACCACCGT GGCAGGCTCG
4701  GATATTAAAG CAACCAGCGG CACCTTGGTT ATTAACGCAA AAGATGCTAA
4751  GCTAAATGGT GATGCATCAG GTGATAGTAC AGAAGTGAAT GCAGTCAACG
4801  ACTGGGGATT TGGTAGTGTG ACTGCGGCAA CCTCAAGCAG TGTGAATATC
4851  ACTGGGGATT TAAACACAGT AAATGGGTTA AATATCATTT CGAAAGATGG
```

FIG.7G.

```
4901  TAGAAACACT GTGCGCTTAA GAGGCAAGGA AATTGAGGTG AAATATATCC
4951  AGCCAGGTGT AGCAAGTGTA GAAGAAGTAA TTGAAGCGAA ACGCGTCCTT
5001  GAAAAAGTAA AAGATTTATC TGATGAAGAA AGAGAAACAT TAGCTAAACT
5051  TGGTGTAAGT GCTGTACGTT TTGTTGAGCC AAATAATACA ATTACAGTCA
5101  ATACACAAAA TGAATTTACA ACCAGACCGT CAAGTCAAGT GATAATTTCT
5151  GAAGGTAAGG CGTGTTTCTC AAGTGGTAAT GGCGCACGAG TATGTACCAA
5201  TGTTGCTGAC GATGGACAGC CGTAGTCAGT AATTGACAAG GTAGATTTCA
5251  TCCTGCAATG AAGTCATTTT ATTTTCGTAT TATTTACTGT GTGGGTTAAA
5301  GTTCAGTACG GGCTTTACCC ATCTTGTAAA AAATTACGGA GAATACAATA
5351  AAGTATTTTT AACAGGTTAT TATTATGAAA AATATAAAAA GCAGATTAAA
5401  ACTCAGTGCA ATATCAGTAT TGCTTGGCCT GGCTTCTTCA TCATTGTATG
5451  CAGAAGAAGC GTTTTTAGTA AAAGGCTTTC AGTTATCTGG TGCACTTGAA
5501  ACTTTAAGTG AAGACGCCCA ACTGTCTGTA GCAAAATCTT TATCTAAATA
5551  CCAAGGCTCG CAAACTTTAA CAAACCTAAA AACAGCACAG CTTGAATTAC
5601  AGGCTGTGCT AGATAAGATT GAGCCAAATA AATTTGATGT GATATTGCCG
5651  CAACAAACCA TTACGGATGG CAATATCATG TTTGAGCTAG TCTCGAAATC
```

FIG.7H.

```
5701  AGCCGCAGAA AGCCAAGTTT TTTATAAGGC GAGCCAGGGT TATAGTGAAG
5751  AAAATATCGC TCGTAGCCTG CCATCTTTGA AACAAGGAAA AGTGTATGAA
5801  GATGGTCGTC AGTGGTTCGA TTTGCGTGAA TTTAATATGG CAAAAGAAAA
5851  CCCGCTTAAG GTTACCCGTG TACATTACGA ACTAAACCCT AAAAACAAAA
5901  CCTCTAATTT GATAATTGCG GGCTTCTCGC CTTTTGGTAA AACGCGTAGC
5951  TTTATTTCTT ATGATAATTT CGGCGCGAGA GAGTTTAACT ACCAACGTGT
6001  AAGCTTGGGT TTTGTTAATG CCAATTTAAC TGGTCATGAT GATGTGTTAA
6151  TTATACCAGT ATGAGTTATG CTGATTCTAA TGATATCGAC GGCTTACCAA
6201  GTGCGATTAA TCGTAAATTA TCAAAAGGTC AATCTATCTC TGCGAATCTG
6251  AAATGGAGTT ATTATCTCCC AACATTTAAC CTTGGCATGG AAGACCAATT
6301  TAAAATTAAT TTAGGCTACA ACTACCGCCA TATTAATCAA ACCTCCGCGT
6351  TAAATCGCTT GGGTGAAACG AAGAAAAAAT TTGCAGTATC AGGCGTAAGT
6401  GCAGGCATTG ATGGACATAT CCAATTTACC CCTAAAACAA TCTTTAATAT
6451  TGATTTAACT CATCATTATT ACGCGAGTAA ATTACCAGGC TCTTTTGGAA
6501  TGGAGCGCAT TGGCGAAACA TTTAATCGCA GCTATCACAT TAGCACAGCC
6551  AGTTTAGGGT TGAGTCAAGA GTTTGCTCAA GGTTGGCATT TTAGCAGTCA
6601  ATTATCAGGT CAATTTACTC TACAAGATAT TAGCAGTATA GATTTATTCT
```

FIG.7I.

```
6651  CTGTAACAGG TACTTATGGC GTCAGAGGCT TTAAATACGG CGGTGCAAGT
6701  GGTGAGCGCG GTCTTGTATG GCGTAATGAA TTAAGTATGC CAAAATACAC
6751  CCGCTTCCAA ATCAGCCCTT ATGCGTTTTA TGATGCAGGT CAGTTCCGTT
6801  ATAATAGCGA AAATGCTAAA ACTTACGGCG AAGATATGCA CACGGTATCC
6851  TCTGCGGGTT TAGGCATTAA AACCTCTCCT ACACAAAACT TAAGCCTAGA
6901  TGCTTTTGTT GCTCGTCGCT TTGCAAATGC CAATAGTGAC AATTTGAATG
6951  GCAACAAAAA ACGCACAAGC TCACCTACAA CCTTCTGGGG GAGATTAACA
7001  TTCAGTTTCT AACCCTGAAA TTTAATCAAC TGGTAAGCGT TCCGCCTACC
7051  AGTTTATAAC TATATGCTTT ACCCGCCAAT TTACAGTCTA TAGGCAACCC
7101  TGTTTTTACC CTTATATATC AAATAAACAA GCTAAGCTGA GCTAAGCAAA
7151  CCAAGCAAAC TCAAGCAAGC CAAGTAATAC TAAAAAAACA ATTTATATGA
7201  TAAACTAAAG TATACTCCAT GCCATGGCGA TACAAGGGAT TTAATAATAT
7251  GACAAAAGAA AATTTGCAAA ACGCTCCTCA AGATGCGACC GCTTTACTTG
7301  CGGAATTAAG CAACAATCAA ACTCCCCTGC GAATATTTAA ACAACCACGC
7351  AAGCCCAGCC TATTACGCTT GGAACAACAT ATCGCAAAAA AAGATTATGA
7401  GTTTGCTTGT CGTGAATTAA TGGTGATTCT GGAAAAAATG GACGCTAATT
```

FIG.7J.

```
7451  TTGGAGGCGT TCACGATATT GAATTTGACG CACCCGCTCA GCTGGCATAT
7501  CTACCCGAAA AATTACTAAT TTATTTTGCC ACTCGTCTCG CTAATGCAAT
7551  TACAACACTC TTTTCCGACC CCGAATTGGC AATTTCTGAA GAAGGGGCGT
7601  TAAAGATGAT TAGCCTGCAA CGCTGGTTGA CGCTGATTTT TGCCTCTTCC
7651  CCCTACGTTA ACGCAGACCA TATTCTCAAT AAATATAATA TCAACCCAGA
7701  TTCCGAAGGT GGCTTTCATT TAGCAACAGA CAACTCTTCT ATTGCTAAAT
7751  TCTGTATTTT TTACTTACCC GAATCCAATG TCAATATGAG TTTAGATGCG
7801  TTATGGGCAG GGAATCAACA ACTTTGTGCT TCATTGTGTT TTGCGTTGCA
7851  GTCTTCACGT TTTATTGGTA CCGCATCTGC GTTTCATAAA AGAGCGGTGG
7901  TTTTACAGTG GTTTCCTAAA AAACTCGCCG AAATTGCTAA TTTAGATGAA
7951  TTGCCTGCAA ATATCCTTCA TGATGTATAT ATGCACTGCA GTTATGATTT
8001  AGCAAAAAAC AAGCACGATG TTAAGCGTCC ATTAAACGAA CTTGTCCGCA
8051  AGCATATCCT CACGCAAGGA TGGCAAGACC GCTACCTTTA CACCTTAGGT
8101  AAAAAGGACG GCAAACCTGT GATGATGGTA CTGCTTGAAC ATTTTAATTC
8151  GGGACATTCG ATTTATCGTA CACATTCAAC TTCAATGATT GCTGCTCGAG
8201  AAAAATTCTA TTTAGTCGGC TTAGGCCATG AGGGCGTTGA TAAAATAGGT
```

FIG.7K.

```
8251  CGAGAAGTGT TTGACGAGTT CTTTGAAATC AGTAGCAATA ATATAATGGA
8301  GAGACTGTTT TTTATCCGTA AACAGTGCGA AACTTTCCAA CCCGCAGTGT
8351  TCTATATGCC AAGCATTGGC ATGGATATTA CCACGATTTT TGTGAGCAAC
8401  ACTCGGCTTG CCCCTATTCA AGCTGTAGCC CTGGGTCATC CTGCCACTAC
8451  GCATTCTGAA TTTATTGATT ATGTCATCGT AGAAGATGAT TATGTGGGCA
8501  GTGAAGATTG TTTCAGCGAA ACCCTTTTAC GCTTACCCAA AGATGCCCTA
8551  CCTTATGTAC CTTCTGCACT CGCCCCACAA AAAGTGGATT ATGTACTCAG
8601  GGAAAACCCT GAAGTAGTCA ATATCGGTAT TGCCGCTACC ACAATGAAAT
8651  TAAACCCTGA ATTTTTGCTA ACATTGCAAG AAATCAGAGA TAAAGCTAAA
8701  GTCAAAATAC ATTTTCATTT CGCACTTGGA CAATCAACAG GCTTGACACA
8751  CCCTTATGTC AAATGGTTTA TCGAAAGCTA TTTAGGTGAC GATGCCACTG
8801  CACATCCCCA CGCACCTTAT CACGATTATC TGGCAATATT GCGTGATTGC
8851  GATATGCTAC TAAATCCGTT TCCTTTCGGT AATACTAACG GCATAATTGA
8901  TATGGTTACA TTAGGTTTAG TTGGTGTATG CAAAACGGGG GATGAAGTAC
8951  ATGAACATAT TGATGAAGGT CTGTTTAAAC GCTTAGGACT ACCAGAATGG
9001  CTGATAGCCG ACACACGAGA AACATATATT GAATGTGCTT TGCGTCTAGC
9051  AGAAAACCAT CAAGAACGCC TTGAACTCCG TCGTTACATC ATAGAAAACA
```

FIG.7L.

```
9101   ACGGCTTACA AAAGCTTTTT ACAGGCGACC CTCGTCCATT GGGCAAAATA
9151   CTGCTTAAGA AAACAAATGA ATGGAAGCGG AAGCACTTGA GTAAAAAATA
9201   ACGGTTTTTT AAAGTAAAAG TGCGGTTAAT TTTCAAAGCG TTTTAAAAAC
9251   CTCTCAAAAA TCAACCGCAC TTTTATCTTT ATAACGATCC CGCACGCTGA
9301   CAGTTTATCA GCCTCCCGCC ATAAAACTCC GCCTTTCATG GCGGAGATTT
9351   TAGCCAAAAC TGGCAGAAAT TAAAGGCTAA AATCACCAAA TTGCACCACA
9401   AAATCACCAA TACCCACAAA AAA
```

FIG.8A.

```
   1  GATCAATCTG GGCGATATTT TTGCCAAAGG TGGTAACATT AATGTCCGCG
  51  CTGCCACTAT TCGCAATAAA GGTAAACTTT CTGCCGACTC TGTAAGCAAA
 101  GATAAAAGTG GTAACATTGT TCTCTCTGCC AAAGAAGGTG AAGCGGAAAT
 151  TGGCGGTGTA ATTTCCGCTC AAAATCAGCA AGCCAAAGGT GGTAAGTTGA
 201  TGATTACAGG CGATAAAGTT ACATTGAAAA CGGGTGCAGT TATCGACCTT
 251  TCGGGTAAAG AAGGGGGAGA AACTTATCTT GGCGGTGACG AGCGTGGCGA
 301  AGGTAAAAAC GGCATTCAAT TAGCAAAGAA AACCACTTTA GAAAAAGGCT
 351  CAACAATTAA TGTGTCAGGT AAAGAAAAAG GTGGGCGCGC TATTGTATGG
 401  GGCGATATTG CGTTAATTGA CGGCAATATT AATGCCCAAG GTAAAGATAT
 451  CGCTAAAACT GGTGGTTTTG TGGAGACGTC GGGGCATTAC TTATCCATTG
 501  ATGATAACGC AATTGTTAAA ACAAAAGAAT GGCTACTAGA CCCAGAGAAT
 551  GTGACTATTG AAGCTCCTTC CGCTTCTCGC GTCGAGCTGG GTGCCGATAG
 601  GAATTCCCAC TCGGCAGAGG TGATAAAAGT GACCCTAAAA AAAAATAACA
 651  CCTCCTTGAC AACACTAACC AATACAACCA TTTCAAATCT TCTGAAAAGT
 701  GCCCACGTGG TGAACATAAC GGCAAGGAGA AAACTTACCG TTAATAGCTC
 751  TATCAGTATA GAAAGAGGCT CCCACTTAAT TCTCCACAGT GAAGGTCAGG
```

FIG.8B.

```
 801  GCGGTCAAGG TGTTCAGATT GATAAAGATA TTACTTCTGA AGGCGGAAAT
 851  TTAACCATTT ATTCTGGCGG ATGGGTTGAT GTTCATAAAA ATATTACGCT
 901  TGGTAGCGGC TTTTTAAACA TCACAACTAA AGAAGGAGAT ATCGCCTTCG
 951  AAGACAAGTC TGGACGGAAC AACCTAACCA TTACAGCCCA AGGGACCATC
1001  ACCTCAGGTA ATAGTAACGG CTTTAGATTT AACAACGTCT CTCTAAACAG
1051  CCTTGGCGGA AAGCTGAGCT TTACTGACAG CAGAGAGGAC AGAGGTAGAA
1101  GAACTAAGGG TAATATCTCA AACAAATTTG ACGGAACGTT AAACATTTCC
1151  GGAACTGTAG ATATCTCAAT GAAAGCACCC AAAGTCAGCT GGTTTTACAG
1201  AGACAAAGGA CGCACCTACT GGAACGTAAC CACTTTAAAT GTTACCTCGG
1251  GTAGTAAATT TAACCTCTCC ATTGACAGCA CAGGAAGTGG CTCAACAGGT
1301  CCAAGCATAC GCAATGCAGA ATTAAATGGC ATAACATTTA ATAAAGCCAC
1351  TTTTAATATC GCACAAGGCT CAACAGCTAA CTTTAGCATC AAGGCATCAA
1401  TAATGCCCTT TAAGAGTAAC GCTAACTACG CATTATTTAA TGAAGATATT
1451  TCAGTCTCAG GGGGGGGTAG CGTTAATTTC AAACTTAACG CCTCATCTAG
1501  CAACATACAA ACCCCTGGCG TAATTATAAA ATCTCAAAAC TTTAATGTCT
1551  CAGGAGGGTC AACTTTAAAT CTCAAGGCTG AAGGTTCAAC AGAAACCGCT
1601  TTTTCAATAG AAAATGATTT AAACTTAAAC GCCACCGGTG GCAATATAAC
```

FIG.8C.

1651 AATCAGACAA GTCGAGGGTA CCGATTCACG CGTCAACAAA GGTGTCGCAG

1701 CCAAAAAAAA CATAACTTTT AAAGGGGGTA ATATCACCTT CGGCTCTCAA

1751 AAAGCCACAA CAGAAATCAA AGGCAATGTT ACCATCAATA AAAACACTAA

1801 CGCTACTCTT CGTGGTGCGA ATTTTGCCGA AAACAAATCG CCTTTAAATA

1851 TAGCAGGAAA TGTTATTAAT AATGGCAACC TTACCACTGC CGGCTCCATT

1901 ATCAATATAG CCGGAAATCT TACTGTTTCA AAAGGCGCTA ACCTTCAAGC

1951 TATAACAAAT TACACTTTTA ATGTAGCCGG CTCATTTGAC AACAATGGCG

2001 CTTCAAACAT TTCCATTGCC AGAGGAGGGG CTAAATTTAA AGATATCAAT

2051 AACACCAGTA GCTTAAATAT TACCACCAAC TCTGATACCA CTTACCGCAC

2101 CATTATAAAA GGCAATATAT CCAACAAATC AGGTGATTTG AATATTATTG

2151 ATAAAAAAAG CGACGCTGAA ATCCAAATTG GCGGCAATAT CTCACAAAAA

2201 GAAGGCAATC TCACAATTTC TTCTGATAAA GTAAATATTA CCAATCAGAT

2251 AACAATCAAA GCAGGCGTTG AAGGGGGGCG TTCTGATTCA AGTGAGGCAG

2301 AAAATGCTAA CCTAACTATT CAAACCAAAG AGTTAAAATT GGCAGGAGAC

2351 CTAAATATTT CAGGCTTTAA TAAAGCAGAA ATTACAGCTA AAATGGCAG

2401 TGATTTAACT ATTGGCAATG CTAGCGGTGG TAATGCTGAT GCTAAAAAAG

FIG.8D.

```
2451  TGACTTTTGA CAAGGTTAAA GATTCAAAAA TCTCGACTGA CGGTCACAAT
2501  GTAACACTAA ATAGCGAAGT GAAAACGTCT AATGGTAGTA GCAATGCTGG
2551  TAATGATAAC AGCACCGGTT TAACCATTTC CGCAAAAGAT GTAACGGTAA
2601  ACAATAACGT TACCTCCCAC AAGACAATAA ATATCTCTGC CGCAGCAGGA
2651  AATGTAACAA CCAAAGAAGG CACAACTATC AATGCAACCA CAGGCAGCGT
2701  GGAAGTAACT GCTCAAAATG GTACAATTAA AGGCAACATT ACCTCGCAAA
2751  ATGTAACAGT GACAGCAACA GAAAATCTTG TTACCACAGA GAATGCTGTC
2801  ATTAATGCAA CCAGCGGCAC AGTAAACATT AGTACAAAAA CAGGGGATAT
2851  TAAAGGTGGA ATTGAATCAA CTTCCGGTAA TGTAAATATT ACAGCGAGCG
2901  GCAATACACT TAAGGTAAGT AATATCACTG GTCAAGATGT AACAGTAACA
2951  GCGGATGCAG GAGCCTTGAC AACTACAGCA GGCTCAACCA TTAGTGCGAC
3001  AACAGGCAAT GCAAATATTA CAACCAAAAC AGGTGATATC AACGGTAAAG
3051  TTGAATCCAG CTCCGGCTCT GTAACACTTG TTGCAACTGG AGCAACTCTT
3101  GCTGTAGGTA ATATTTCAGG TAACACTGTT ACTATTACTG CGGATAGCGG
3151  TAAATTAACC TCCACAGTAG GTTCTACAAT TAATGGGACT AATAGTGTAA
3201  CCACCTCAAG CCAATCAGGC GATATTGAAG GTACAATTTC TGGTAATACA
3251  GTAAATGTTA CAGCAAGCAC TGGTGATTTA ACTATTGGAA ATAGTGCAAA
```

FIG.8E.

```
3301  AGTTGAAGCG AAAAATGGAG CTGCAACCTT AACTGCTGAA TCAGGCAAAT
3351  TAACCACCCA AACAGGCTCT AGCATTACCT CAAGCAATGG TCAGACAACT
3401  CTTACAGCCA AGGATAGCAG TATCGCAGGA AACATTAATG CTGCTAATGT
3451  GACGTTAAAT ACCACAGGCA CTTTAACTAC TACAGGGGAT TCAAAGATTA
3501  ACGCAACCAG TGGTACCTTA ACAATCAATG CAAAAGATGC CAAATTAGAT
3551  GGTGCTGCAT CAGGTGACCG CACAGTAGTA AATGCAACTA ACGCAAGTGG
3601  CTCTGGTAAC GTGACTGCGA AAACCTCAAG CAGCGTGAAT ATCACCGGGG
3651  ATTTAAACAC AATAAATGGG TTAAATATCA TTTCGGAAAA TGGTAGAAAC
3701  ACTGTGCGCT TAAGAGGCAA GGAAATTGAT GTGAAATATA TCCAACCAGG
3751  TGTAGCAAGC GTAGAAGAGG TAATTGAAGC GAAACGCGTC CTTGAGAAGG
3801  TAAAAGATTT ATCTGATGAA GAAAGAGAAA CACTAGCCAA ACTTGGTGTA
3851  AGTGCTGTAC GTTTCGTTGA GCCAAATAAT GCCATTACGG TTAATACACA
3901  AAACGAGTTT ACAACCAAAC CATCAAGTCA AGTGACAATT TCTGAAGGTA
3951  AGGCGTGTTT CTCAAGTGGT AATGGCGCAC GAGTATGTAC CAATGTTGCT
4001  GACGATGGAC AGCAGTAGTC AGTAATTGAC AAGGTAGATT TCATCCTGCA
4051  ATGAAGTCAT TTTATTTTCG TATTATTTAC TGTGTGGGTT AAAGTTCAGT
```

FIG.8F.

```
4101  ACGGGCTTTA CCCACCTTGT AAAAAATTAC GAAAAATACA ATAAAGTATT
4151  TTTAACAGGT TATTATTATG AAAAACATAA AAAGCAGATT AAAACTCAGT
4201  GCAATATCAA TATTGCTTGG CTTGGCTTCT TCATCGACGT ATGCAGAAGA
4251  AGCGTTTTTA GTAAAAGGCT TTCAGTTATC TGGCGCG
```

FIG.9A.

```
  1  GGGAATGAGC GTCGTACACG GTACAGCAAC CATGCAAGTA GACGGCAATA
 51  AAACCACTAT CCGTAATAGC GTCAATGCTA TCATCAATTG GAAACAATTT
101  AACATTGACC AAAATGAAAT GGAGCAGTTT TTACAAGAAA GCAGCAACTC
151  TGCCGTTTTC AACCGTGTTA CATCTGACCA AATCTCCCAA TTAAAAGGGA
201  TTTTAGATTC TAACGGACAA GTCTTTTTAA TCAACCCAAA TGGTATCACA
251  ATAGGTAAAG ACGCAATTAT TAACACTAAT GGCTTTACTG CTTCTACGCT
301  AGACATTTCT AACGAAAACA TCAAGGCGCG TAATTTCACC CTTGAGCAAA
351  CCAAGGATAA AGCACTCGCT GAAATCGTGA ATCACGGTTT AATTACCGTT
401  GGTAAAGACG GTAGCGTAAA CCTTATTGGT GGCAAAGTGA AAAACGAGGG
451  CGTGATTAGC GTAAATGGCG GTAGTATTTC TTTACTTGCA GGGCAAAAAA
501  TCACCATCAG CGATATAATA AATCCAACCA TCACTTACAG CATTGCTGCA
551  CCTGAAAACG AAGCGATCAA TCTGGGCGAT ATTTTTGCCA AAGGTGGTAA
601  CATTAATGTC CGCGCTGCCA CTATTCGCAA TAAAGGTAAA CTTTCTGCCG
651  ACTCTGTAAG CAAAGATAAA AGTGGTAACA TTGTTCTCTC TGCCAAAGAA
701  GGTGAAGCGG AAATTGGCGG TGTAATTTCC GCTCAAAATC AGCAAGCCAA
751  AGGTGGTAAG TTGATGATTA CAGGTGATAA AGTCACATTA AAAACAGGTG
```

FIG.9B.

```
 801  CAGTTATCGA CCTTTCAGGT AAAGAAGGGG GAGAGACTTA TCTTGGCGGT
 851  GATGAGCGTG GCGAAGGTAA AAATGGTATT CAATTAGCGA AGAAAACCTC
 901  TTTAGAAAAA GGCTCGACAA TTAATGTATC AGGCAAAGAA AAAGGCGGGC
 951  GCGCTATTGT ATGGGGCGAT ATTGCATTAA TTAATGGTAA CATTAATGCT
1001  CAAGGTAGCG ATATTGCTAA AACTGGCGGC TTTGTGGAAA CATCAGGACA
1051  TGACTTATCC ATTGGTGATG ATGTGATTGT TGACGCTAAA GAGTGGTTAT
1101  TAGACCCAGA TGATGTGTCC ATTGAAACTC TTACATCTGG ACGCAATAAT
1151  ACCGGCGAAA ACCAAGGATA TACAACAGGA GATGGGACTA AAGAGTCACC
1201  TAAAGGTAAT AGTATTTCTA AACCTACATT AACAAACTCA ACTCTTGAGC
1251  AAATCCTAAG AAGAGGTTCT TATGTTAATA TCACTGCTAA TAATAGAATT
1301  TATGTTAATA GCTCCATCAA CTTATCTAAT GGCAGTTTAA CACTTCACAC
1351  TAAACGAGAT GGAGTTAAAA TTAACGGTGA TATTACCTCA AACGAAAATG
1401  GTAATTTAAC CATTAAAGCA GGCTCTTGGG TTGATGTTCA TAAAAACATC
1451  ACGCTTGGTA CGGGTTTTTT GAATATTGTC GCTGGGGATT CTGTAGCTTT
1501  TGAGAGAGAG GGCGATAAAG CACGTAACGC AACAGATGCT CAAATTACCG
1551  CACAAGGGAC GATAACCGTC AATAAAGATG ATAAACAATT TAGATTCAAT
1601  AATGTATCTA TTAACGGGAC GGGCAAGGGT TTAAAGTTTA TTGCAAATCA
```

FIG.9C.

```
1651  AAATAATTTC ACTCATAAAT TTGATGGCGA AATTAACATA TCTGGAATAG
1701  TAACAATTAA CCAAACCACG AAAAAAGATG TTAAATACTG GAATGCATCA
1751  AAAGACTCTT ACTGGAATGT TTCTTCTCTT ACTTTGAATA CGGTGCAAAA
1801  ATTTACCTTT ATAAAATTCG TTGATAGCGG CTCAAATTCC CAAGATTTGA
1851  GGTCATCACG TAGAAGTTTT GCAGGCGTAC ATTTTAACGG CATCGGAGGC
1901  AAAACAAACT TCAACATCGG AGCTAACGCA AAAGCCTTAT TTAAATTAAA
1951  ACCAAACGCC GCTACAGACC CAAAAAAAGA ATTACCTATT ACTTTTAACG
2001  CCAACATTAC AGCTACCGGT AACAGTGATA GCTCTGTGAT GTTTGACATA
2051  CACGCCAATC TTACCTCTAG AGCTGCCGGC ATAAACATGG ATTCAATTAA
2101  CATTACCGGC GGGCTTGACT TTTCCATAAC ATCCCATAAT CGCAATAGTA
2151  ATGCTTTTGA AATCAAAAAA GACTTAACTA TAAATGCAAC TGGCTCGAAT
2201  TTTAGTCTTA AGCAAACGAA AGATTCTTTT TATAATGAAT ACAGCAAACA
2251  CGCCATTAAC TCAAGTCATA ATCTAACCAT TCTTGGCGGC AATGTCACTC
2301  TAGGTGGGGA AAATTCAAGC AGTAGCATTA CGGGCAATAT CAATATCACC
2351  AATAAAGCAA ATGTTACATT ACAAGCTGAC ACCAGCAACA GCAACACAGG
2401  CTTGAAGAAA AGAACTCTAA CTCTTGGCAA TATATCTGTT GAGGGGAATT
```

FIG.9D.

```
2451  TAAGCCTAAC TGGTGCAAAT GCAAACATTG TCGGCAATCT TTCTATTGCA
2501  GAAGATTCCA CATTTAAAGG AGAAGCCAGT GACAACCTAA ACATCACCGG
2551  CACCTTTACC AACAACGGTA CCGCCAACAT TAATATAAAA CAAGGAGTGG
2601  TAAAACTCCA AGGCGATATT ATCAATAAAG GTGGTTTAAA TATCACTACT
2651  AACGCCTCAG GCACTCAAAA AACCATTATT AACGGAAATA TAACTAACGA
2701  AAAAGGCGAC TTAAACATCA AGAATATTAA AGCCGACGCC GAAATCCAAA
2751  TTGGCGGCAA TATCTCACAA AAAGAAGGCA ATCTCACAAT TTCTTCTGAT
2801  AAAGTAAATA TTACCAATCA GATAACAATC AAAGCAGGCG TTGAAGGGGG
2851  GCGTTCTGAT TCAAGTGAGG CAGAAAATGC TAACCTAACT ATTCAAACCA
2901  AAGAGTTAAA ATTGGCAGGA GACCTAAATA TTTCAGGCTT TAATAAAGCA
2951  GAAATTACAG CTAAAAATGG CAGTGATTTA ACTATTGGCA ATGCTAGCGG
3001  TGGTAATGCT GATGCTAAAA AAGTGACTTT TGACAAGGTT AAAGATTCAA
3051  AAATCTCGAC TGACGGTCAC AATGTAACAC TAAATAGCGA AGTGAAAACG
3101  TCTAATGGTA GTAGCAATGC TGGTAATGAT AACAGCACCG GTTTAACCAT
3151  TTCCGCAAAA GATGTAACGG TAAACAATAA CGTTACCTCC CACAAGACAA
3201  TAAATATCTC TGCCGCAGCA GGAAATGTAA CAACCAAAGA AGGCACAACT
3251  ATCAATGCAA CCACAGGCAG CGTGGAAGTA ACTGCTCAAA ATGGTACAAT
```

FIG.9E.

```
3301  TAAAGGCAAC ATTACCTCGC AAAATGTAAC AGTGACAGCA ACAGAAAATC
3351  TTGTTACCAC AGAGAATGCT GTCATTAATG CAACCAGCGG CACAGTAAAC
3401  ATTAGTACAA AAACAGGGGA TATTAAAGGT GGAATTGAAT CAACTTCCGG
3451  TAATGTAAAT ATTACAGCGA GCGGCAATAC ACTTAAGGTA AGTAATATCA
3501  CTGGTCAAGA TGTAACAGTA ACAGCGGATG CAGGAGCCTT GACAACTACA
3551  GCAGGCTCAA CCATTAGTGC GACAACAGGC AATGCAAATA TTACAACCAA
3601  AACAGGTGAT ATCAACGGTA AAGTTGAATC CAGCTCCGGC TCTGTAACAC
3651  TTGTTGCAAC TGGAGCAACT CTTGCTGTAG GTAATATTTC AGGTAACACT
3701  GTTACTATTA CTGCGGATAG CGGTAAATTA ACCTCCACAG TAGGTTCTAC
3751  AATTAATGGG ACTAATAGTG TAACCACCTC AAGCCAATCA GGCGATATTG
3801  AAGGTACAAT TTCTGGTAAT ACAGTAAATG TTACAGCAAG CACTGGTGAT
3851  TTAACTATTG GAAATAGTGC AAAAGTTGAA GCGAAAAATG GAGCTGCAAC
3901  CTTAACTGCT GAATCAGGCA AATTAACCAC CCAAACAGGC TCTAGCATTA
3951  CCTCAAGCAA TGGTCAGACA ACTCTTACAG CCAAGGATAG CAGTATCGCA
4001  GGAAACATTA ATGCTGCTAA TGTGACGTTA AATACCACAG GCACTTTAAC
4051  TACTACAGGG GATTCAAAGA TTAACGCAAC CAGTGGTACC TTAACAATCA
```

FIG.9F.

```
4101  ATGCAAAAGA TGCCAAATTA GATGGTGCTG CATCAGGTGA CCGCACAGTA
4151  GTAAATGCAA CTAACGCAAG TGGCTCTGGT AACGTGACTG CGAAAACCTC
4201  AAGCAGCGTG AATATCACCG GGGATTTAAA CACAATAAAT GGGTTAAATA
4251  TCATTTCGGA AAATGGTAGA AACACTGTGC GCTTAAGAGG CAAGGAAATT
4301  GATGTGAAAT ATATCCAACC AGGTGTAGCA AGCGTAGAAG AGGTAATTGA
4351  AGCGAAACGC GTCCTTGAGA AGGTAAAAGA TTTATCTGAT GAAGAAAGAG
4401  AAACACTAGC CAAACTTGGT GTAAGTGCTG TACGTTTCGT TGAGCCAAAT
4451  AATGCCATTA CGGTTAATAC ACAAAACGAG TTTACAACCA AACCATCAAG
4501  TCAAGTGACA ATTTCTGAAG GTAAGGCGTG TTTCTCAAGT GGTAATGGCG
4551  CACGAGTATG TACCAATGTT GCTGACGATG GACAGCAGTA GTCAGTAATT
4601  GACAAGGTAG ATTTCATCCT GCAATGAAGT CATTTTATTT TCGTATTATT
4651  TACTGTGTGG GTTAAAGTTC AGTACGGGCT TTACCCACCT TGTAAAAAAT
4701  TA
```

FIG.10A. COMPARISON OF DERIVED AMINO ACID SEQUENCE

```
          1                                                  50
Hmw3com   .......... .......... .......... .......... ..........
Hmw4com   .......... .......... .......... .......... ..........
Hmw1com   MNKIYRLKFS KRLNALVAVS ELARGCDHST EKGSEKPARM KVRHLALKPL
Hmw2com   MNKIYRLKFS KRLNALVAVS ELARGCDHST EKGSEKPARM KVRHLALKPL

          51                                                 100
Hmw3com   .......... .......... .......... .......... ..........
Hmw4com   .......... .......... ..GMSVVHGT ATMQVDGNKT TIRNSVNAII
Hmw1com   SAMLLSLGVT SIPQSVLASG LQGMSVVHGT ATMQVDGNKT TIRNSVNAII
Hmw2com   SAMLLSLGVT SIPQSVLASG LQGMSVVHGT ATMQVDGNKT TIRNSVNAII

          101                                                150
Hmw3com   .......... .......... .......... .......... ..........
Hmw4com   NWKQFNIDQN EMEQFLQESS NSAVFNRVTS DQISQLKGIL DSNGQVFLIN
```

FIG.10B.

```
Hmw1com   NWKQFNIDQN EMVQFLQENN NSAVFNRVTS NQISQLKGIL DSNGQVFLIN
Hmw2com   NWKQFNIDQN EMVQFLQENN NSAVFNRVTS NQISQLKGIL DSNGQVFLIN

          151                                                 200
Hmw3com   .......... .......... .......... .......... ..........
Hmw4com   PNGITIGKDA IINTNGFTAS TLDISNENIK ARNFTLEQTK DKALAEIVNH
Hmw1com   PNGITIGKDA IINTNGFTAS TLDISNENIK ARNFTLEQTK DKALAEIVNH
Hmw2com   PNGITIGKDA IINTNGFTAS TLDISNENIK ARNFTLEQTK DKALAEIVNH

          201                                                 250
Hmw3com   .......... .......... .......... .......... ..........
Hmw4com   GLITVGKDGS VNLIGGKVKN EGVISVNGGS ISLLAGQKIT ISDIINPTIT
Hmw1com   GLITVGKDGS VNLIGGKVKN EGVISVNGGS ISLLAGQKIT ISDIINPTIT
Hmw2com   GLITVGKDGS VNLIGGKVKN EGVISVNGGS ISLLAGQKIT ISDIINPTIT

          251                                                 300
Hmw3com   .......... INLGDIFAKG GNINVRAATI RNKGKLSADS VSKDKSGNIV
```

FIG.10C.

```
Hmw4com   YSIAAPENEA INLGDIFAKG GNINVRAATI RNKGKLSADS VSKDKSGNIV
Hmw1com   YSIAAPENEA VNLGDIFAKG GNINVRAATI RNKGKLSADS VSKDKSGNIV
Hmw2com   YSIAAPENEA VNLGDIFAKG GNINVRAATI RNKGKLSADS VSKDKSGNIV

                301                                           350
Hmw3com   LSAKEGEAEI GGVISAQNQQ AKGGKLMITG DKVTLKTGAV IDLSGKEGGE
Hmw4com   LSAKEGEAEI GGVISAQNQQ AKGGKLMITG DKVTLKTGAV IDLSGKEGGE
Hmw1com   LSAKEGEAEI GGVISAQNQQ AKGGKLMITG DKVTLKTGAV IDLSGKEGGE
Hmw2com   LSAKEGEAEI GGVISAQNQQ AKGGKLMITG DKVTLKTGAV IDLSGKEGGE

                351                                           400
Hmw3com   TYLGGDERGE GKNGIQLAKK TTLEKGSTIN VSGKEKGGRA IVWGDIALID
Hmw4com   TYLGGDERGE GKNGIQLAKK TTLEKGSTIN VSGKEKGGRA IVWGDIALID
Hmw1com   TYLGGDERGE GKNGIQLAKK TTLEKGSTIN VSGKEKGGRA IVWGDIALID
Hmw2com   TYLGGDERGE GKNGIQLAKK TTLEKGSTIN VSGKEKGGRA IVWGDIALID
```

FIG.10D.

```
          401                                                  450
Hmw3com   GNINAQGK.D IAKTGGFVET SGHYLSIDDN AIVKTKEWLL DPENVTIEAP
Hmw4com   GNINAQGS.D IAKTGGFVET SGHDLSIGDD VIVDAKEWLL DPDDVSIETL
Hmw1com   GNINAQGSGD IAKTGGFVET SGHDLFIKDN AIVDAKEWLL DPDNVTINAE
Hmw2com   GNINAQGSGD IAKTGGFVET SGHYLSIESN AIVKTKEWLL DPDDVTIEAE

          451                                                  500
Hmw3com   SASRVELGAD RNSHSAEVIK VTLKKNNTSL TTLTNTTISN LLKSAHVVNI
Hmw4com   TSGRNNTGEN QGYTTGDGTK ESPKGNSISK PTLTNSTLEQ ILRRGSYVNI
Hmw1com   TAGRSNTSED DEYTGSGNSA STPKRNKE.K TTLTNTTLES ILKKGTFVNI
Hmw2com   DPLRNNTGIN DEFPTGTGEA SDPKKNSELK TTLTNTTISN YLKNAWTMNI

          501                                                  550
Hmw3com   TARRKLTVNS SISIERGSHL ILHSEGQGGQ GVQIDKDITS .E...GGNLT
Hmw4com   TANNRIYVNS SINLSNGS.L TLHTK...RD GVKINGDITS NE...NGNLT
Hmw1com   TANQRIYVNS SINL.SNGSL TLWSEGRSGG GVEINNDITT GDDTRGANLT
Hmw2com   TASRKLTVNS SINGSNGSHL ILHSKGQRGG GVQIDGDIT. ...SKGGNLT
```

FIG.10E.

```
          551                                                    600
Hmw3com   IYSGGWVDVH KNITLGS.GF LNITTKEGDI AFEDKSGR..  ..NNLTITAQ
Hmw4com   IKAGSWVDVH KNITLGT.GF LNIVAGDS.V AFEREGDKAR NATDAQITAQ
Hmw1com   IYSGGWVDVH KNISLGAQGN INITAKQD.I AFEKGSNQV.  ......ITGQ
Hmw2com   IYSGGWVDVH KNITLD.QGF LNITA.AS.V AFEGGNNKAR DANNLTITAQ

          601                                                    650
Hmw3com   GTITSG.NSN GFRFNNVSLN SLGGKLSFTD SREDRGRRTK GNISNKFDGT
Hmw4com   GTITVNKDDK QFRFNNVSIN GTGKGLKFIA NQN.......  .NFTHKFDGE
Hmw1com   GTIT.SGNQK GFRFNNVSLN GTGSGLQFTT KRTN.....K YAITNKFEGT
Hmw2com   GTVTITGEGK DFRANNVSLN GTGKGLNIIS SVNN......  ..LTHNLSGT

          651                                                    700
Hmw3com   LNISGTVDIS MKAPKVSWFY RD.KGRTYWN VTTLNVTSGS KFNLSIDSTG
Hmw4com   INISGIVTIN QTTKKDVKYW NA.SKDSYWN VSSLTLNTVQ KFTF.IKFVD
Hmw1com   LNISGKVNIS MVLPKNESGY DKFKGRTYWN LTSLNVSESG EFNLTIDSRG
```

FIG.10F.

```
Hmw2com   INISGNITIN QTTRKNTSYW QTSHD.SHWN VSALNLETGA NFTF.IKYIS

          701                                                 750
Hmw3com   SGSTG...PS IRNA..ELNG ITFN....KA TFNIAQGSTA NFSIKASIMP
Hmw4com   SGSNS...QD LRSSRRSFAG VHFNGIGGKT NFNIGANAKA LFKLKPNAAT
Hmw1com   SDSAGTLTQ. ....PYNLNG ISFN...KDT TFNVERNARV NFDIKAPIGI
Hmw2com   SNSKGLTTQY RSSAGVNFNG V..N...GNM SFNLKEGAKV NFKLKPNENM

          751                                                 800
Hmw3com   FKSNANYAL. FNEDISVSG. .GGSVNFKLN ASSSNIQTPG VIIKSQNFNV
Hmw4com   DPKKELPIT. FNANITATGN SDSSVMFDIH A...NLTSRA AGINMDSINI
Hmw1com   NKYSSLNYAS FNGNISVSG. .GGSVDFTLL ASSSNVQTPG VVINSKYFNV
Hmw2com   NTSKPLPI.R FLANITATG. .GGSVFFDIY ANHS...GRG AELKMSEINI

          801                                                 850
Hmw3com   SGGSTLNLKA EGSTETAFSI ENDLNLNATG GNITIRQVEG T..DSRVNKG
Hmw4com   TGGLDFSITS HNRNSNAFEI KKDLTINATG SNFSLKQTKD SFYNEYSKHA
```

FIG.10G.

```
Hmw1com   STGSSLRFKT SGSTKTGFSI EKDLTLNATG GNITLLQVEG T..DGMIGKG
Hmw2com   SNGANFTLNS HVRGDDAFKI NKDLTINATN SNFSLRQTKD DFYDGYARNA

          851                                                 900
Hmw3com   VAAKKNITFK GGNITFGSQK ATTEIKGNVT INKNTNATLR GANFAEN...
Hmw4com   INSSHNLTIL GGNVTLGGEN SSSSITGNIN ITNKANVTLQ ADTSNSNTGL
Hmw1com   IVAKKNITFE GGNITFGSRK AVTEIEGNVT INNNANVTLI GSDFDNHQ..
Hmw2com   INSTYNISIL GGNVTLGGQN SSSSITGNIT IEKAANVTLE ANNAPNQQNI

          901                                                 950
Hmw3com   KSPLNIAGNV INNGNLTTAG SIINIAGNLT VSKGANLQAI TNYTFNVAGS
Hmw4com   KKRTLTLGNI SVEGNLSLTG ANANIVGNLS IAEDSTFKGE ASDNLNITGT
Hmw1com   KPLTIKKDVI INSGNLTAGG NIVNIAGNLT VESNANFKAI TNFTFNVGGL
Hmw2com   RDRVIKLGSL LVNGSLSLTG ENADIKGNLT ISESATFKGK TRDTLNITGN

          951                                                1000
```

FIG.10H.

```
Hmw3com   FDNNGASNIS IARGGAKFK. DINNTSSLNI TTNSDTTYRT IIKGNISNKS
Hmw4com   FTNNGTANIN IKQGVVKLQG DINNKGGLNI TTNASGTQKT IINGNITNEK
Hmw1com   FDNKGNSNIS IAKGGARFK. DIDNSKNLSI TTNSSSTYRT IISGNITNKN
Hmw2com   FTNNGTAEIN ITQGVVKLG. NVTNDGDLNI TTHAKRNQRS IIGGDIINNK

          1001                                              1050
Hmw3com   GDLNIIDKKS DAEIQIGGNI SQKEGNLTIS SDKVNITNQI TIKAGVEGGR
Hmw4com   GDLNIKNIKA DAEIQIGGNI SQKEGNLTIS SDKVNITNQI TIKAGVEGGR
Hmw1com   GDLNITNEGS DTEMQIGGDI SQKEGNLTIS SDKINITKQI TIKAGVDGEN
Hmw2com   GSLNITDSNN DAEIQIGGNI SQKEGNLTIS SDKINITKQI TIKKGIDGED

          1051                                              1100
Hmw3com   SDSSEAENAN LTIQTKELKL AGDLNISGFN KAEITAKNGS DLTIGNASGG
Hmw4com   SDSSEAENAN LTIQTKELKL AGDLNISGFN KAEITAKNGS DLTIGNASGG
Hmw1com   SDSDATNNAN LTIKTKELKL TQDLNISGFN KAEITAKDGS DLTIGNTNSA
Hmw2com   SSSDATSNAN LTIKTKELKL TEDLSISGFN KAEITAKDGR DLTIGNSNDG
```

FIG.10I.

```
          1101                                                    1150
Hmw3com   N..ADAKKVT FDKVKDSKIS TDGHNVTLNS EVKT..SNGS SNAGNDNSTG
Hmw4com   N..ADAKKVT FDKVKDSKIS TDGHNVTLNS EVKT..SNGS SNAGNDNSTG
Hmw1com   D.GTNAKKVT FNQVKDSKIS ADGHKVTLHS KVETSGSNNN TEDSSDNNAG
Hmw2com   NSGAEAKKVT FNNVKDSKIS ADGHNVTLNS KVKTSSSNGG RESNSDNDTG

          1151                                                    1200
Hmw3com   LTISAKDVTV NNNVTSHKTI NISAAAGNVT TKEGTTINAT TGSVEVTAQN
Hmw4com   LTISAKDVTV NNNVTSHKTI NISAAAGNVT TKEGTTINAT TGSVEVTAQN
Hmw1com   LTIDAKNVTV NNNITSHKAV SISATSGEIT TKTGTTINAT TGNVEIT...
Hmw2com   LTITAKNVEV NKDVTSLKTV NITA.SEKVT TTAGSTINAT NGKASIT...

          1201                                                    1250
Hmw3com   GTIKGNITSQ NVTVTATENL VTTENAVINA TSGTVNISTK TGDIKGGIES
Hmw4com   GTIKGNITSQ NVTVTATENL VTTENAVINA TSGTVNISTK TGDIKGGIES
Hmw1com   .......... .......... .......... ........AQ TGDIKGGIES
```

FIG.10J.

```
Hmw2com   .......... .......... .......... ........TK T.........

          1251                                                1300
Hmw3com   TSGNVNITAS GNTLKVSNIT GQDVTVTADA GALTTTAGST ISATTGNANI
Hmw4com   TSGNVNITAS GNTLKVSNIT GQDVTVTADA GALTTTAGST ISATTGNANI
Hmw1com   SSGSVTLTAT EGALAVSNIS GNTVTVTANS GALTTLAGST IKG.TESVTT
Hmw2com   .......... .......... .......... .......... ..........

          1301                                                1350
Hmw3com   TTKTGDINGK VESSSGSVTL VATGATLAVG NISGNTVTIT ADSGKLTSTV
Hmw4com   TTKTGDINGK VESSSGSVTL VATGATLAVG NISGNTVTIT ADSGKLTSTV
Hmw1com   SSQSGDIG.. .......... .........G TISGGTVEVK ATESLTTQSN
Hmw2com   ....GDIS.. .......... .........G TISGNTVSVS ATVDLTTKSG

          1351                                                1400
Hmw3com   GSTINGTNSV TTSSQSGDIE GTISGNTVNV TASTGDLTIG NSAKVEAKNG
Hmw4com   GSTINGTNSV TTSSQSGDIE GTISGNTVNV TASTGDLTIG NSAKVEAKNG
```

FIG.10K.

```
Hmw1com   SKIKATTGEA NVTSATGTIG GTISGNTVNV TANAGDLTVG NGAEINATEG
Hmw2com   SKIEAKSGEA NVTSATGTIG GTISGNTVNV TANAGDLTVG NGAEINATEG

          1401                                              1450
Hmw3com   AATLTAESGK LTTQTGSSIT SSNGQTTLTA KDSSIAGNIN AANVTLNTTG
Hmw4com   AATLTAESGK LTTQTGSSIT SSNGQTTLTA KDSSIAGNIN AANVTLNTTG
Hmw1com   AATLTTSSGK LTTEASSHIT SAKGQVNLSA QDSSVAGSIN AANVTLNTTG
Hmw2com   AATLTATGNT LTTEAGSSIT STKGQVDLLA QNSSIAGNIN AANVTLNTTG

          1451                                              1500
Hmw3com   TLTTTGDSKI NATSGTLTIN AKDAKLDGAA SGDRTVVNAT NASGSGNVTA
Hmw4com   TLTTTGDSKI NATSGTLTIN AKDAKLDGAA SGDRTVVNAT NASGSGNVTA
Hmw1com   TLTTVKGSNI NATSGTLTIN AKDAELNGAA LGNHTVVNAT NANGSGSVIA
Hmw2com   TLTTVAGSDI KATSGTLTIN AKDAKLNGDA SGDSTEVNAV NASGSGSVTA

          1501                                              1550
```

FIG.10L.

```
Hmw3com   KTSSSVNITG DLNTINGLNI ISENGRNTVR LRGKEIDVKY IQPGVASVEE
Hmw4com   KTSSSVNITG DLNTINGLNI ISENGRNTVR LRGKEIDVKY IQPGVASVEE
Hmw1com   TTSSRVNITG DLITINGLNI ISKNGINTVL LKGVKIDVKY IQPGIASVDE
Hmw2com   ATSSSVNITG DLNTVNGLNI ISKDGRNTVR LRGKEIEVKY IQPGVASVEE

            1551                                            1600
Hmw3com   VIEAKRVLEK VKDLSDEERE TLAKLGVSAV RFVEPNNAIT VNTQNEFTTK
Hmw4com   VIEAKRVLEK VKDLSDEERE TLAKLGVSAV RFVEPNNAIT VNTQNEFTTK
Hmw1com   VIEAKRILEK VKDLSDEERE ALAKLGVSAV RFIEPNNTIT VDTQNEFATR
Hmw2com   VIEAKRVLEK VKDLSDEERE TLAKLGVSAV RFVEPNNTIT VNTQNEFTTR

            1601                        1632
Hmw3com   PSSQVTISEG KACFSSGNGA RVCTNVADDG QQ
Hmw4com   PSSQVTISEG KACFSSGNGA RVCTNVADDG QQ
Hmw1com   PLSRIVISEG RACFSNSDGA TVCVNIADNG R.
Hmw2com   PSSQVIISEG KACFSSGNGA RVCTNVADDG QP
```

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/02550

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 39/02
US CL :424/92

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/92; 435/851

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Gene-Seq, APS, Biosis, Embase, Scisearch, Chem Abstracts

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Pediatric Infectious Disease Journal, Volume 9, No. 5, issued 05 May 1990, Barenkamp et al, "Development of Serum Bactericidal Activity Following Nontypable Haemophilus influenzae Acute Otitis Media", pages 333-339, see page 337.	1-3
Y	Pediatric Research, Volume 29, No. 4 part 2, issued 1991, Barenkamp S. J., "DNA Sequence Analysis of Genes for Nontypable Haemophilus influenza High Molecular Weight Outer Membrane Proteins which are Targets of Bactericidal Antibody", see page 167A, column 1, abstract no. 985.	1-3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"P"	document published prior to the international filing date but later than the priority date claimed		

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